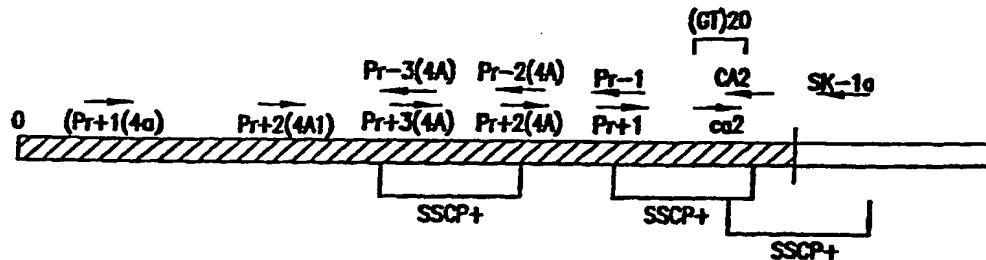




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(54) Title: NUCLEIC ACIDS, KITS, AND METHODS FOR THE DIAGNOSIS, PROGNOSIS AND TREATMENT OF GLAUCOMA AND RELATED DISORDERS



## (57) Abstract

In a preferred aspect of the invention, the upstream sequences of the TIGR protein encoding sequence can be used to diagnose a sensitivity to steroids and a risk for glaucoma or ocular hypertensive disorders. Methods, kits, and nucleic acids containing polymorphisms, base substitutions, or base additions located within the upstream region and within protein-encoding regions of the TIGR gene are also provided. The upstream sequences disclosed, including the TIGR promoter regions and those regions possessing functional characteristics associated with or possessed by the TIGR gene 5' regulatory region, can also be used to generate cells, vectors, transgenic animals, and nucleic acid constructs useful in a variety of diagnostic and prognostic methods and kits as well as therapeutic compounds, compositions and methods.

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## NUCLEIC ACIDS, KITS, AND METHODS FOR THE DIAGNOSIS, PROGNOSIS AND TREATMENT OF GLAUCOMA AND RELATED DISORDERS

### FIELD OF THE INVENTION

5 The present invention relates to the field of diagnostic and prognostic methods and kits, treatments, and compositions useful in understanding and identifying glaucoma, related intraocular pressure-disorders, and steroid sensitivity.

### CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Patent Application serial no. 10 09/227,881, filed January 11, 1999, specifically incorporated by reference herein, which is a continuation-in-part of U.S. Patent Application serial no. 08/938,669, filed September 26, 1997, specifically incorporated by reference herein, which is a continuation-in-part of U.S. Patent Application serial no. 08/791,154, filed January 28, 1997, also specifically incorporated by reference herein.

15 BACKGROUND OF THE INVENTION

A group of debilitating eye diseases, the "Glaucomas" represent the leading cause of preventable blindness in the United States and other developed nations. In general, glaucomas are characterized by the alteration of the trabecular meshwork (TM), which consists of specialized endothelial cells and their associated connective tissue. The TM endothelial cells line 20 the path the aqueous humor of the eye filters through during the normal, physiological flux. The cells generate and regulate the TM by producing extracellular molecules, the composition of which is thought to directly control the aqueous fluid flow.

In Primary Open Angle Glaucoma ("POAG"), the most common form of glaucoma, an alteration in the TM leads to an obstruction of the normal ability of aqueous humor to leave its 25 chamber surrounding the iris. However, the specific cells in the chamber between the iris and the cornea, in a region called the iridocorneal angle, remain "open" in that they continue to allow the egress of aqueous fluid (see, Vaughan, D. *et al.*, In: *General Ophthalmology*, Appleton & Lange, Norwalk, CT, pp. 213-230 (1992); and *Gray's Anatomy*, 37<sup>th</sup> Ed., Churchill Livingstone, London, pp. 1180-1190 (1989)). As a result of the alteration in the TM and the obstruction, an 30 increased intraocular pressure ("IOP") can be observed. IOP can result in progressive visual loss and blindness if not treated appropriately and in a timely fashion.

Glaucomas are estimated to affect between 0.4% and 3.3% of all adults over 40 years old (Leske, M.C. *et al.*, *Amer. J. Epidemiol.* 113:1843-1846 (1986); Bengtsson, B., *Br. J. Ophthalmol.* 73:483-487 (1989); Strong, N.P., *Ophthal. Physiol. Opt.* 12:3-7 (1992)). Moreover, the prevalence of the disease rises to over 6% of those 75 years or older (Strong, N.P., *Ophthal. Physiol. Opt.* 12:3-7 (1992)).

A link between steroid, corticosteroid, or glucocorticoid treatments and the increased IOP found in POAG disease has long been suspected. While only 5% of the normal population have high IOP increases in response to topical glucocorticoids, greater than 40-50% of similarly treated patients with POAG show a high IOP increase (16 mm Hg). In addition, an Open Angle Glaucoma may be induced by exposure to glucocorticoids. This observation has suggested that an increased or abnormal glucocorticoid response in trabecular cells of the TM may be involved in POAG (Zhan, G.L. *et al.*, *Exper. Eye Res.* 54:211-218 (1992); Yun, A.J. *et al.*, *Invest. Ophthalmol. Vis. Sci.* 30:2012-2022 (1989); Clark, A.F., *Exper. Eye Res.* 55:265 (1992); Klemetti, A., *Acta Ophthalmol.* 68:29-33 (1990); Knepper, P.A., U.S. Patent No. 4,617,299).

The ability of glucocorticoids to induce a glaucoma-like condition has led to efforts to identify genes or gene products induced by the cells of the trabecular meshwork in response (Polansky, J.R. *et al.*, In: *Glaucoma Update IV*, Springer-Verlag, Berlin, pp. 20-29 (1991); Polansky J.R. and Weinrob, R.N., In: *Handbook of Experimental Pharmacology*, Vol. 69, Springer-Verlag, Berlin, pp. 461-538 (1984)). Initial efforts using short-term exposure to dexamethasone revealed only changes in specific protein synthesis. Extended exposure to relatively high levels of dexamethasone was, however, found to induce the expression of related 66 kD and 55 kD proteins that could be visualized by gel electrophoresis (Polansky, J.R. *et al.*, In: *Glaucoma Update IV*, Springer-Verlag, Berlin, pp. 20-29 (1991)). The induction kinetics of these proteins as well as their dose response characteristics were similar to the kinetics that were required for steroid-induced IOP elevation in human subjects (Polansky, J.R. *et al.*, In: *Glaucoma Update IV*, Springer-Verlag, Berlin, pp. 20-29 (1991)). Problems of aggregation and apparent instability or loss of protein in the purification process were obstacles in obtaining a direct protein sequence.

Nguyen *et al.*, U.S. Patent Application No: 08/649,432, filed May 17, 1996, now U.S. Patent No. 5,789,169, the entire disclosure of which is hereby incorporated by reference as if set forth at length herein, disclosed a novel protein sequence (the TIGR, trabecular meshwork inducible glucocorticoid response protein) highly induced by glucocorticoids in the endothelial lining cells of the human trabecular meshwork. Nguyen *et al.* also disclosed the cDNA sequence for that protein, the protein itself, molecules that bind to it, and nucleic acid molecules that

encode it, and provided improved methods and reagents for diagnosing glaucoma and related disorders, as well as for diagnosing other diseases or conditions, such as cardiovascular, immunological, or other diseases or conditions that affect the expression or activity of the protein.

Because increased IOP is a readily measurable characteristic of glaucoma, the diagnosis of the disease is largely screened for by measuring intraocular pressure (tonometry) (Strong, N.P., *Ophthal. Physiol. Opt.* 12:3-7 (1992), Greve, M. et al., *Can. J. Ophthalmol.* 28:201-206 (1993)). Unfortunately, because glaucomatous and normal pressure ranges overlap, such methods are of limited value unless multiple readings are obtained (Hitchings, R.A., *Br. J. Ophthalmol.* 77:326 (1993); Tuck, M.W. et al., *Ophthal. Physiol. Opt.* 13:227-232 (1993); Vaughan, D. et al., In: *General Ophthalmology*, Appleton & Lange, Norwalk, CT, pp. 213-230 (1992); Vernon, S.A., *Eye* 7:134-137 (1993)). Patients may also have a differential sensitivity to optic nerve damage at a given IOP. For these reasons, additional methods, such as direct examination of the optic disk and determination of the extent of a patient's visual field loss are often conducted to improve the accuracy of diagnosis (Greve, M. et al., *Can. J. Ophthalmol.* 28:201- 206 (1993)). Moreover, these techniques are of limited prognostic value. In some aspects, the present invention fulfills the need for improved diagnostic and prognostic methods.

The elevation of intraocular pressure (IOP) due to topical corticosteroids (and other routes of administration) is an important clinical problem that limits the clinical use of these effective anti-inflammatory agents. If not observed in sufficient time, the IOP elevation (especially in certain individuals who show the high end of steroid-induced IOP elevations) can result in optic nerve damage and permanent visual field loss, termed "steroid glaucoma." Even patients taking inhaled, nasal, rectal, and facial steroids may be at risk. The present invention, in part, provides improved diagnostic agents, prognostic agents, therapeutic agents and methods that address this clinical problem.

### SUMMARY OF THE INVENTION

The invention relates to nucleic acids, genes, proteins and cells that can be used in the treatment, diagnosis, prognosis, and identification of glaucoma, IOP-related disorders, or steroid sensitivity. The invention encompasses numerous agents, compositions, and methods, some of which are described by the objects and aspects of the invention detailed below. Others can be devised from the entire contents of this disclosure, and from the detailed description that follows.

In one aspect, the invention relates to nucleic acids comprising non-coding regions or promoter regions associated with the TIGR (trabecular meshwork inducible glucocorticoid

response) gene of mammals. These nucleic acids can be used in identifying polymorphisms in the genomes of mammals and humans that predict steroid sensitivity or a susceptibility to glaucomas or diseases related to alterations in IOP. A number of diagnostic or prognostic methods and kits can be designed from these nucleic acids.

- 5 In one embodiment, the nucleic acids can be used to identify or detect a single base polymorphism in a genome. In other embodiments, two or more single base polymorphisms or multiple base polymorphisms can be identified or detected. The detection of a known polymorphism can be the basis for diagnostic and prognostic methods and kits of the invention. Various methods of detecting nucleic acids can be used in these methods and with the kits,  
10 including, but not limited to, solution hybridization, hybridization to microarrays containing immobilized nucleic acids or other immobilized nucleic acids, amplification-based methods such as PCR and the like, and an appropriate biosensor apparatus comprising a nucleic acid or nucleic acid binding reagent.

- 15 In another aspect, the invention relates to specific sequences and variants or mutants from the promoter or 5' regulatory region of the human TIGR gene and nucleic acids incorporating these sequences, variants or mutants. The nucleic acids can be incorporated into the methods and kits of the invention, or used in expression systems, vectors, and cells to produce a protein or polypeptide of interest, or used in methods to identify or detect regulatory proteins or proteins that specifically bind to promoter or regulatory regions of the TIGR gene. While many of the  
20 examples below detail work from human tissue, other animals may be used as a source of the sequences.

- 25 In one embodiment of this aspect of the invention, for example, nucleic acids having the disclosed TIGRmt11 sequence variant, represented by the change at nucleotide 5113 in SEQ ID NO: 1, 3, or 34 from T to C, or the change in nucleotide 5117 in SEQ ID NO: 2 from T to C. The presence of sequence variant mt11 is linked to the high IOP response to steroid treatments and a nucleic acid incorporating the singe base substitution can be used to identify and determine individuals at risk for developing glaucoma from undergoing a steroid treatment therapy, or a progression from an ocular hypertensive state, or those with a steroid sensitivity. And, because of the link between high IOP responses to steroids and the later development of glaucoma,  
30 nucleic acids having the TIGRmt11 sequence variant may also be used to identify the risk of developing glaucomas, such as POAG. The identification of changes in IOP can be done by any known means, however, the "Armaly" criteria is preferred (see Armaly, M.F., *Arch. Ophthalmol.* 70:492 (1963); Armaly, M.F., *Arch Ophthalmol.* 75:32-35 (1966); Kitazawa, Y. et al., *Arch. Ophthalmol.* 99:819-823 (1981); Lewis, J.M. et al., *Amer. J. Ophthalmol.* 106:607-612 (1988);

Becker, B. et al. Amer. J.Ophthalmol. 57:543 (1967), all of which are specifically incorporated herein by reference in their entireties).

An object of the invention is to provide a method for diagnosing glaucoma in a patient which comprises the steps: (A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, said marker nucleic acid molecule comprising a nucleotide sequence of a polynucleotide that specifically hybridizes to a polynucleotide that is linked to a TIGR promoter, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient, wherein nucleic acid hybridization between said marker nucleic acid molecule, and said complementary nucleic acid molecule obtained from said patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting TIGR response in said patient; (B) permitting hybridization between said marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient; and (C) detecting the presence of said polymorphism, wherein the detection of the polymorphism is diagnostic of glaucoma.

Another object of the invention is to provide a method for prognosing glaucoma in a patient which comprises the steps: (A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, said marker nucleic acid molecule comprising a nucleotide sequence of a polynucleotide that specifically hybridizes to a polynucleotide that is linked to a TIGR promoter, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient, wherein nucleic acid hybridization between said marker nucleic acid molecule, and said complementary nucleic acid molecule obtained from said patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting TIGR response in said patient; (B) permitting hybridization between said marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient; and (C) detecting the presence of said polymorphism, wherein the detection of the polymorphism is prognostic of glaucoma.

Another object of the invention is to provide marker nucleic acid molecules capable of specifically detecting *TIGRmt1*, *TIGRmt2*, *TIGRmt3*, *TIGRmt4*, *TIGRmt5*, *TIGRmt11* and *TIGRsv1*.

Another object of the invention is to provide a method for diagnosing steroid sensitivity in a patient which comprises the steps: (A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, the marker nucleic acid molecule comprising a nucleotide sequence of a polynucleotide that is linked to a TIGR promoter, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of the patient, wherein nucleic acid hybridization between the marker nucleic acid molecule, and the complementary nucleic acid molecule obtained from the patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting TIGR response in the patient; (B) permitting hybridization between said TIGR-encoding marker nucleic acid molecule and the complementary nucleic acid

molecule obtained from the patient; and (C) detecting the presence of the polymorphism, wherein the detection of the polymorphism is diagnostic of steroid sensitivity.

Further objects of the invention provide a nucleic acid molecule that comprises the sequence of SEQ ID NO: 1 or 34, recombinant DNA molecules containing a polynucleotide that specifically hybridizes to SEQ ID NO: 1 or 34 and substantially purified molecules that specifically bind to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 1 or 34.

Further objects of the invention provide a nucleic acid molecule that comprises the sequence of SEQ ID NO: 3, recombinant DNA molecules containing a polynucleotide that specifically hybridizes to SEQ ID NO: 3 and substantially purified molecules that specifically bind to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 3.

Additional objects of the invention provide a nucleic acid molecule that comprises the sequence of SEQ ID NO: 4, recombinant DNA molecules containing a polynucleotide that specifically hybridizes to SEQ ID NO: 4 and substantially purified molecules that specifically bind to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 4.

Additional objects of the invention provide a nucleic acid molecule that comprises the sequence of SEQ ID NO: 5, recombinant DNA molecules containing a polynucleotide that specifically hybridizes to SEQ ID NO: 5 and substantially purified molecules that specifically bind to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 5.

An additional object of the present invention is to provide a method of treating glaucoma which comprises administering to a glaucomatous patient an effective amount of an agent that inhibits the synthesis of a TIGR protein.

Indeed, the molecules of the present invention may be used to diagnose diseases or conditions which are characterized by alterations in the expression of extracellular proteins.

#### BRIEF DESCRIPTION OF THE FIGURES:

Figures 1A, 1B, 1C, 1D and 1E provide the nucleic acid sequence of a TIGR promoter region (SEQ ID NO: 1) from an individual without glaucoma.

Figures 2A, 2B, 2C and 2D provide the location and sequence changes highlighted in bold associated with glaucoma mutants *TIGRmt1*, *TIGRmt2*, *TIGRmt3*, *TIGRmt4*, *TIGRmt5*, *TIGRmt11*, and *TIGRsv1* (SEQ ID NO: 2).

Figures 3A, 3B, 3C, 3D, 3E, 3F, and 3G provide nucleic acid sequences of a TIGR promoter, and TIGR exons, TIGR introns and TIGR downstream sequences (SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5).

Figure 4 provides a diagrammatic representation of the location of primers on the TIGR gene promoter for Single Strand Conformational Polymorphism (SSCP) analysis.

Figure 5 provides a diagrammatic representation of the TIGR exons and the arrangement of SSCP primers.

Figure 6 provides a homology analysis of TIGR homology with olfactomedin and olfactomedin-related proteins.

5 Figure 7 shows the nucleotide sequence of TIGR (SEQ ID NO: 26).

Figure 8 shows the amino acid sequence of TIGR (SEQ ID NO: 32).

10 Figure 9 shows the results of a gel shift assay and a diagrammatic representation of the results. Lanes labeled "TM" represent the binding of cellular components from human trabecular meshwork cells to the 283 base pair TIGR 5' regulatory region. Lanes labeled "HeLa" represent the binding of cellular components from HeLa cells to the same nucleic acid. A much higher amount of cellular component binds in the +DEX (dexamethasone) treated TM cells than in the -DEX Tm cells (no dexamethasone).

## DETAILED DESCRIPTION OF THE INVENTION

### I. Agents of the Invention

15 As used herein, the term "glaucoma" has its art recognized meaning, and includes both primary glaucomas, secondary glaucomas, juvenile glaucomas, congenital glaucomas, and familial glaucomas, including, without limitation, pigmentary glaucoma, high tension glaucoma and low tension glaucoma and their related diseases. The methods of the present invention are particularly relevant to the diagnosis of POAG, OAG, juvenile glaucoma, and inherited 20 glaucomas. The methods of the present invention are also particularly relevant to the prognosis of POAG, OAG, juvenile glaucoma, and inherited glaucomas. A disease or condition is said to be related to glaucoma if it possesses or exhibits a symptom of glaucoma, for example, an increased intra-ocular pressure resulting from aqueous outflow resistance (see, Vaughan, D. *et al.*, In: *General Ophthalmology*, Appleton & Lange, Norwalk, CT, pp. 213-230 (1992)). The preferred 25 agents of the present invention are discussed in detail below.

The agents of the present invention are capable of being used to diagnose the presence or severity of glaucoma and its related diseases in a patient suffering from glaucoma (a "glaucomatous patient"). The agents of the present invention are also capable of being used to prognose the presence or severity of glaucoma and its related diseases in a person not yet 30 suffering from any clinical manifestations of glaucoma. Such agents may be either naturally occurring or non-naturally occurring. As used herein, a naturally occurring molecule may be "substantially purified," if desired, such that one or more molecules that is or may be present in a naturally occurring preparation containing that molecule will have been removed or will be present at a lower concentration than that at which it would normally be found.

The agents of the present invention will preferably be "biologically active" with respect to either a structural attribute, such as the capacity of a nucleic acid to hybridize to another nucleic acid molecule, or the ability of a protein to be bound by antibody (or to compete with another molecule for such binding). Alternatively, such an attribute may be catalytic, and thus involve 5 the capacity of the agent to mediate a chemical reaction or response.

As used herein, the term "TIGR protein" refers to a protein having the amino acid sequence of SEQ ID NO: 32. As used herein, the agents of the present invention comprise nucleic acid molecules, proteins, and organic molecules.

As indicated above, the trabecular meshwork has been proposed to play an important role 10 in the normal flow of the aqueous, and has been presumed to be the major site of outflow resistance in glaucomatous eyes. Human trabecular meshwork (HTM) cells are endothelial like cells which line the outflow channels by which aqueous humor exits the eye; altered synthetic function of the cells may be involved in the pathogenesis of steroid glaucoma and other types of 15 glaucoma. Sustained steroid treatment of these cells are interesting because it showed that a major difference was observed when compared to 1-2 day glucocorticoid (GC) exposure. This difference appears relevant to the clinical onset of steroid glaucoma (1-6 weeks).

Although trabecular meshwork cells had been found to induce specific proteins in response to glucocorticoids (see, Polansky, J.R., In: "*Basic Aspects of Glaucoma Research III*", Schattauer, New York 307-318 (1993)), efforts to purify the expressed protein were encumbered 20 by insolubility and other problems. Nguyen, T.D. *et al.*, (In: "*Basic Aspects of Glaucoma Research III*", Schattauer, New York, 331-343 (1993), herein incorporated by reference) used a molecular cloning approach to isolate a highly induced mRNA species from glucocorticoid-induced human trabecular cells. The mRNA exhibited a time course of induction that was similar to the glucocorticoid-induced proteins. The clone was designated "II.2" (ATCC No: 25 97994, American Type Culture Collection, Manassas, VA).

Nguyen *et al.*, U.S. Patent Application No: 08/649,432 filed May 17, 1996, isolated a II.2 clone which encoded a novel secretory protein that is induced in cells of the trabecular meshwork upon exposure to glucocorticoids. It has been proposed that this protein may become deposited in the extracellular spaces of the trabecular meshwork and bind to the surface of the endothelial 30 cells that line the trabecular meshwork, thus causing a decrease in aqueous flow. Quantitative dot blot analysis and PCR evaluations have shown that the mRNA exhibits a progressive induction with time whereas other known GC-inductions from other systems and found in HTM cells (metallothionein, alpha-1 acid glycoprotein and alpha-1 antichymotrypsin) reached maximum level at one day or earlier. Of particular interest, the induction level of this clone was 35 very high (4-6% total cellular mRNA) with control levels undetectable without PCR method. Based on studies of  $^{35}\text{S}$  methionine cell labeling, the clone has the characteristics recently

discovered for the major GC-induced extracellular glycoprotein in these cells, which is a sialenated, N-glycosylated molecule with a putative inositol phosphate anchor. The induction of mRNA approached 4% of the total cellular mRNA. The mRNA increased progressively over 10 days of dexamethasone treatment. The IL2 clone is 2.0 Kb whereas the Northern blotting shows  
5 a band of 2.5 Kb. Although not including a poly A tail, the 3' end of the clone contains two consensus polyadenylation signals.

A genomic clone was isolated and designated P<sub>1</sub>TIGR clone (ATCC No: 97570, American Type Culture Collection, Rockville, Maryland). In-situ hybridization using the P<sub>1</sub>TIGR clone shows a TIGR gene and/or a sequence or sequences that specifically hybridize to  
10 the TIGR gene located at chromosome 1, q21-27, and more preferably to the TIGR gene located at chromosome 1, q22-26, and most preferably to the TIGR gene located at chromosome 1, q24. Clone P<sub>1</sub>TIGR comprises human genomic sequences that specifically hybridize to the TIGR gene cloned into the BamHI site of vector pCYPAC (Ioannou *et al.*, *Nature Genetics*, 6:84-89 (1994) herein incorporated by reference).

15 As used herein, the term "TIGR gene" refers to the region of DNA involved in producing a TIGR protein; it includes, without limitation, regions preceding and following the coding region as well as intervening sequences between individual coding regions.

As used herein, the term "TIGR exon" refers to any interrupted region of the TIGR gene  
20 that serves as a template for a mature TIGR mRNA molecule. As used herein, the term "TIGR intron" refers to a region of the TIGR gene which is non-coding and serves as a template for a TIGR mRNA molecule.

Localization studies using a Stanford G3 radiation hybrid panel mapped the TIGR gene near the D1S2536 marker with a LOD score of 6.0 (Richard *et al.*, *American Journal of Human Genetics* 52.5: 915-921 (1993), herein incorporated by reference); Frazer *et al.*, *Genomics* 14.3:  
25 574-578 (1992), herein incorporated by reference; Research Genetics, Huntsville, Alabama). Other markers in this region include: D1S210; D1S1552; D1S2536; D1S2790; SHGC-12820; and D1S2558.

Sequences located upstream of the TIGR coding region are isolated and sequenced in a non-glaucomic individual. The upstream sequence is set forth in SEQ ID. No. 1 and 34.  
30 Sequence comparisons of the upstream region of a non-glaucoma individual and individuals with glaucoma identify a number of mutations in individuals with glaucoma. Some of these mutations are illustrated in Figure 2, the sequence of which can be used to identify the exact changes in the human genomic sequences from the upstream region of the TIGR gene disclosed here (SEQ ID NO: 1, 2, 3, and 34). SEQ ID NO: 3 includes the regions through the start of transcription and  
35 the start of translation, as evident from a sequence comparison to the figures. SEQ ID NO: 34 ends before the transcription start site, again as evident from a sequence comparison with the

figures. Six mutations are specifically disclosed here. *TIGRmt1* is the result of a replacement of a cytosine with a guanine at position 4337 (SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3). *TIGRmt2* is the result of a replacement of a cytosine with a thymine at position 4950 (SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3). *TIGRmt3* is the result of an addition in the following order of a guanine, a thymine, a guanine, and a thymine (GTGT) at position 4998 (SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3). *TIGRmt4* is the result of a replacement of an adenine with a guanine at position 4256 (SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3). *TIGRmt5* is the result of a replacement of a guanine with an adenine at position 4262 (SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3). *TIGRmt11* (not pictured in Figure 2) is the result of a replacement of a thymine with a cytosine at position 5113 (SEQ ID NO: 1, 3, or 34) and at the equivalent position in SEQ ID NO: 2, at nucleotide 5117. One or more of *TIGRmt1*, *TIGRmt2*, *TIGRmt3*, *TIGRmt4*, *TIGRmt5*, and *TIGTmt11* can be homozygous or heterozygous.

Sequence comparisons of the upstream region of a non-glaucoma individual and individuals with glaucoma identify at least one sequence variation in individuals with glaucoma. One such sequence variant is illustrated in Figure 2. *TIGRsv1* is the result of a replacement of an adenine with a guanine at position 4406 (SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3). Also, the presence of *TIGRmt11* is associated with steroid sensitivity or an increased susceptibility to developing glaucoma or IOP-related disorders during steroid or corticosteroid treatment.

Molecules comprising sequences upstream of the TIGR coding region provide useful markers for polymorphic studies. Such molecules include primers suitable for single strand conformational polymorphic studies, examples of which are as follows: forward primer "Sk-1a": 5'-TGA GGC TTC CTC TGG AAA C-3' (SEQ ID NO: 6); reverse primer "ca2": 5'-TGA AAT CAG CAC ACC AGT AG-3' (SEQ ID NO: 7); forward primer "CA2": 5'-GCA CCC ATA CCC CAA TAA TAG-3' (SEQ ID NO: 8); reverse primer "Pr+1": 5'-AGA GTT CCC CAG ATT TCA CC-3' (SEQ ID NO: 9); forward primer "Pr-1": 5'-ATC TGG GGA ACT CTT CTC AG-3' (SEQ ID NO: 10); reverse primer "Pr+2(4A2)": 5'-TAC AGT TGT TGC AGA TAC G-3' (SEQ ID NO: 11); forward primer "Pr-2(4A)": 5'-ACA ACG TAT CTG CAA CAA CTG-3' (SEQ ID NO: 12); reverse primer "Pr+3(4A)": 5'-TCA GGC TTA ACT GCA GAA CC-3' (SEQ ID NO: 13); forward primer "Pr-3(4A)": 5'-TTG GTT CTG CAG TTA AGC C-3' (SEQ ID NO: 14); reverse primer "Pr+2(4A1)": 5'-AGC AGC ACA AGG GCA ATC C-3' (SEQ ID NO: 15); reverse primer "Pr+1(4A)": 5'-ACA GGG CTA TAT TGT GGG-3' (SEQ ID NO: 16).

In addition, molecules comprising sequences within TIGR exons provide useful markers for polymorphic studies. Such molecules include primers suitable for single strand conformational polymorphic studies, examples of which are as follows: forward primer "KS1X": 5'-CCT GAG ATG CCA GCT GTC C-3' (SEQ ID NO: 17); reverse primer "SK1XX": 5'-CTG

AAG CAT TAG AAG CCA AC-3' (SEQ ID NO: 18); forward primer "KS2a1": 5'-ACC TTG GAC CAG GCT GCC AG-3' (SEQ ID NO: 19); reverse primer "SK3" 5'-AGG TTT GTT CGA GTT CCA G-3' (SEQ ID NO: 20); forward primer "KS4": 5'-ACA ATT ACT GGC AAG TAT GTT CCA G-3' (SEQ ID NO: 21); reverse primer "SK6A": 5'-CCT TCT CAG CCT TGC TAC C-3' GG-3' (SEQ ID NO: 22); forward primer "KS5": 5'-ACA CCT CAG CAG ATG CTA CC-3' (SEQ ID NO: 23); reverse primer "SK8": 5'-ATG GAT GAC TGA CAT GGC C-3' (SEQ ID NO: 24); forward primer "KS6": 5'-AAG GAT GAA CAT GGT CAC C-3' (SEQ ID NO: 25).

The locations of primers: Sk-1a, ca2, CA2, Pr+1, Pr-1, Pr+2(4A2), Pr-2(4A), Pr+3(4A), Pr-3(4A), Pr-3(4A), Pr+2(4A1), and Pr+1(4A) are diagrammatically set forth in Figure 4. The location of primers: KS1X, SK1XX, Ks2a1, SK3, KS4, SK6A, KS5, SK8, and KS6 are diagrammatically set forth in Figure 5.

The primary structure of the TIGR coding region initiates from an ATG initiation site (SEQ ID NO:3, residues 5337-5339) and includes a 20 amino acid consensus signal sequence a second ATG (SEQ ID NO: 3, residues 5379-5381), indicating that the protein is a secretory protein. The nucleotide sequence for the TIGR coding region is depicted in Figure 7 (SEQ ID NO: 26). The protein contains an N-linked glycosylation site located in the most hydrophilic region of the molecule. The amino terminal portion of the protein is highly polarized and adopts alpha helical structure as shown by its hydropathy profile and the Garnier-Robison structure analysis. In contrast, the protein contains a 25 amino acid hydrophobic region near its carboxy terminus. This region may comprise a glucocorticoid-induced protein (GIP) anchoring sequence. The amino acid sequence of TIGR is depicted in Figure 8 (SEQ ID NO: 32).

Study of cyclohexamide treatment in the absence and presence of GC suggest that the induction of TIGR may involve factors in addition to the GC receptor. The TIGR gene may be involved in the cellular stress response since it is also induced by stimulants such as H<sub>2</sub>O<sub>2</sub>, 12-O-tetradecanoylphorbol-13-acetate (TPA), and high glucose; this fact may relate to glaucoma pathogenesis and treatment.

A preferred class of agents comprises TIGR nucleic acid molecules ("TIGR molecules") or fragments thereof. Such molecules may be either DNA or RNA. A second preferred class of agents ("TIGR molecules") comprises the TIGR protein, its peptide fragments, fusion proteins, and analogs.

TIGR nucleic acid molecules or fragments thereof are capable of specifically hybridizing to other nucleic acid molecules under certain circumstances. As used herein, two nucleic acid molecules are said to be capable of specifically hybridizing to one another if the two molecules are capable of forming an anti-parallel, double-stranded nucleic acid structure. A nucleic acid molecule is said to be the "complement" of another nucleic acid molecule if the molecules exhibit complete complementarity. As used herein, molecules are said to exhibit "complete

complementarity" when every nucleotide of one of the molecules is complementary to a nucleotide of the other. Two molecules are said to be "minimally complementary" if they can hybridize to one another with sufficient stability to permit them to remain annealed to one another under at least conventional "low-stringency" conditions. Similarly, the molecules are 5 said to be "complementary" if they can hybridize to one another with sufficient stability to permit them to remain annealed to one another under conventional "high-stringency" conditions. Conventional stringency conditions are described by Sambrook et al., In: Molecular Cloning, A Laboratory Manual, 2nd Edition, Cold Spring Harbor Press, Cold Spring Harbor, New York (1989)), and by Haymes et al., In: Nucleic Acid Hybridization, A Practical Approach, IRL Press, 10 Washington, DC (1985), the entirety of which is herein incorporated by reference. Departures from complete complementarity are therefore permissible, as long as such departures do not completely preclude the capacity of the molecules to form a double-stranded structure. In order for an nucleic acid molecule to serve as a primer or probe it need only be sufficiently complementary in sequence to be able to form a stable double-stranded structure under the 15 particular solvent and salt concentrations employed.

Appropriate stringency conditions which promote DNA hybridization, for example, 6.0 x sodium chloride/sodium citrate (SSC) at about 45°C, followed by a wash of 2.0 x SSC at 50°C, are known to those skilled in the art or can be found in Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. For example, the salt concentration in the wash 20 step can be selected from a low stringency of about 2.0 x SSC at 50°C to a high stringency of about 0.2 x SSC at 50°C. In addition, the temperature in the wash step can be increased from low stringency conditions at room temperature, about 22°C, to high stringency conditions at about 65°C. Both temperature and salt may be varied, or either the temperature or the salt concentration may be held constant while the other variable is changed.

In a preferred embodiment, a nucleic acid of the present invention will specifically hybridize to one or more of the nucleic acid molecules set forth in SEQ ID NO: 1-5 or 34, or complements thereof, or fragments of about 20 to about 200 bases of either, under moderately stringent conditions, for example at about 2.0 x SSC and about 65°C. In a particularly preferred embodiment, a nucleic acid of the present invention will specifically hybridize to one or more of the nucleic acid molecules set forth in SEQ ID NO: 1-5 or 34, or complements or fragments of either under high stringency conditions. 25

In one aspect of the present invention, a preferred marker nucleic acid molecule of the present invention has the nucleic acid sequence set forth in SEQ ID NO: 6-25 or 33, or complements thereof or fragments of either. In another aspect of the present invention, a preferred marker nucleic acid molecule of the present invention shares between about 80% to 30 about 100% or about 90% to about 100% sequence identity with the nucleic acid sequence set

forth in SEQ ID NO: 6 –25 or 33, or complement thereof or fragments of either. In a further aspect of the present invention, a preferred marker nucleic acid molecule of the present invention shares between about 95% to about 100% sequence identity with the sequence set forth in SEQ ID NO: 6-25 or 33, or complement thereof or fragments of either. In a more preferred aspect of the present invention, a preferred marker nucleic acid molecule of the present invention shares between 98% and about 100% sequence identity with the nucleic acid sequence set forth in SEQ ID NO:6-25 or 33, or complement thereof or fragments of either.

Regulatory Regions and Agents that Bind to the Regions or Agents that Alter the Binding of a Molecule that Binds to the Regions

Sequence comparisons of the upstream region identify a number of DNA motifs (*cis* elements) or regulatory regions. These DNA motifs or *cis* elements are shown in Figure 1. These motifs include, without limitation, glucocorticoid response motif(s), shear stress response motif(s), NF $\kappa$ B recognition motif(s), and AP1 motif(s). The locations of these and other motifs, discussed below, are diagrammatically set forth in Figure 1.

As used herein, the term “*cis* elements capable of binding” refers to the ability of one or more of the described *cis* elements to specifically bind an agent. Such binding may be by any chemical, physical or biological interaction between the *cis* element and the agent, including, but not limited, to any covalent, steric, agostic, electronic and ionic interaction between the *cis* element and the agent. As used herein, the term “specifically binds” refers to the ability of the agent to bind to a specified *cis* element but not to wholly unrelated nucleic acid sequences. Regulatory region refers to the ability of a nucleic acid fragment, region or length to functionally perform a biological activity. The biological activity may be binding to the nucleic acid specific DNA sequence. The biological activity may also modulate, enhance, inhibit or alter the transcription of a nearby coding region. The biological activity may be identified by a gel shift assay, in which binding to a nucleic acid fragment can be detected. Other methods of detecting the biological activity in a nucleic acid regulatory region are known in the art (*see Current Protocols in Molecular Biology*, for example).

In an embodiment to identify or detect regulatory proteins or proteins or compounds that specifically bind to promoter or regulatory regions of the TIGR gene, a number of vector systems employing reporter genes can be useful. The promoter or 5' regulatory regions can be linked to control expression of the reporter gene so that the presence of the reporter gene indicates the transcriptional activity from the promoter or 5' regulatory region. The DNA constructs, vectors, and cells made for this aspect of the invention, and the methods employing them, can be useful in a variety of ways. For example, they can detect the presence or absence of tissue-specific factors

that modulate TIGR gene expression. Modulating expression can mean increasing or decreasing transcription, increasing or decreasing translation, or otherwise effecting the amount of TIGR mRNA or protein present in a cell. They can also be used to identify compounds that affect TIGR gene expression, IOP-related disorders, or steroid sensitivity. These identified compounds 5 can then be used to development therapeutic or diagnostic treatments, especially for glaucoma and IOP-related disorders.

The types of expression systems and reporter genes that can be used or adapted for use are well known in the art. For example, vectors containing genes for a luciferase activity, an alkaline phosphatase activity, or a green fluorescent protein activity are commonly used. See 10 Ausubel *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), and supplements through May 1999. Inserting a 5' regulatory region of the TIGR gene into a vector of this type puts the expression of the reporter gene under the control of the TIGR sequence. The vector or vectors can then be inserted into various cell types to examine differences in tissue specific expression, which can then lead to identification of tissue specific factors that modulate 15 TIGR expression as well as compounds that affect the activity of the tissue specific factors. The vectors can also be used to detect compounds that affect the transcription modulating activity of a TIGR 5' regulatory region. Alternatively, the 5' regulatory region and reporter gene constructs can be used in homologous recombination techniques to produce cells. When properly inserted 20 into the genome of a cell, the reporter gene will be under the control of the TIGR regulatory region. Homologously recombinant cells can than be used, as discussed above, to detect changes in and modulation of expression due to various treatments or in separate cells.

For example, human trabecular meshwork cells (HTM) can be transiently or permanently transfected with a vector containing various 5' regulatory sequences from the TIGR gene that control expression of an alkaline phosphatase activity (AP). The expression of AP, or change in 25 expression versus a control, indicates the presence of transcription-modulating sequences. By comparing the expression in HTM cells with the expression in other cells, such as Cos or HeLa cells, one can detect the presence of cell-specific compounds that influence transcriptional activity from the TIGR gene. Also, by treating the cells with test compounds, one can detect a compound that affects transcription.

30 Additionally, once cell types have been characterized for the presence of expression modulating activity, further uses of the 5' regulatory regions can identify the presence of specific DNA binding by cellular components or proteins within particular cells. Assays and methods for detection DNA binding include, but are not limited to, gel shift assays and equivalent techniques known in the art. In gel shift assays, the presence of a compound that binds to a DNA is detected 35 by observing a shift in the mobility of the DNA through an agarose, polyacrylamide, or other gel matrix. Thus, by running the DNA through the gel in the presence of one or more cellular

components or cell extracts and comparing to controls, specific binding to the DNA can be detected. In a similar way, various compounds can be tested for their ability to affect binding of a cellular component to the DNA by treating the sample with one or more test compounds before running the DNA through the gel. Of course, the cells used in these assays need not be primary cultured cells or established cell lines. Any type of manipulated cell can be used, even those where deliberate changes to DNA binding proteins or transcription factors contained in the cell have been made.

The TIGR gene sequences that may be used in the DNA constructs, cells, vectors, or in methods for detecting useful promoter regions, tissue or cell-specific components that bind TIGR gene sequences, or in the related methods to detect compounds affecting DNA binding or promoter activity, can be large, for example at least as big as 1.6 kb, or much smaller, on the order of about 10 to 300 bp. A preferred region is the 283 bp region from 5340 to 5044 of SEQ ID NO: 3, designated SEQ ID NO: 37, or a 227 bp region from 5044 to 5271 (end) of SED ID NO: 34, which is identified as SEQ ID NO: 38.

Other preferred regions are identified in the Figures and SEQ IDs listed or are inherently disclosed by comparing the Figures and SEQ IDs. To illustrate, the TATA boxes in SEQ ID NO: 3 and 34 both start at position 5232. Particular regions from SEQ ID NO: 3 and 34 can be correlated with the identified regulatory regions in Figure 1, where the TATA box begins at 5230. Thus, additional preferred 5' regions can incorporate one or more regulatory regions identified and discussed herein as well as the many sequence variations given in the consensus regulatory sequences listed in Figure 1. For example, SEQ ID NO: 37 can be changed at various places in the nGRE-Prl regulatory sequence, beginning at base 39 of SEQ ID NO: 37, to coincide with the consensus sequence given in Figure 1. Base 67 of SEQ ID NO: 37 can be changed from T to G, and bases 57 and 65 from C to A. These changes would not effect the basic regulatory activity of these sequences, but may affect the degree of regulatory modulation possible. Similar substitutions using any one or more of the listed regulatory regions can be made to a region from SEQ ID NO: 1-3, or 34. Also, substitutions that incorporate one or more of the mutant sequences identified herein may also be made. For example, base 69 of SEQ ID NO: 37 can be changed from a T to a C to correlate with the TIGR.mt11 mutant herein. Numerous variants in the 5' regulatory regions incorporating one or both of the consensus sequences changes and the changes from the identified TIGR mutants can be made. Bases may also be added or deleted without effecting the region's basic ability to modulate expression.

The following discussion identifies some of the regulatory regions identified in the TIGR 5' region or other well known regulatory activities. As noted, these regions or sequences, or variants of them, can be incorporated into the DNA constructs, vectors, cells, and methods of the invention. Any combination of them, with or without the above identified regions in SEQ ID

NO: 37 and 18, or variants thereof, can be tested for the ability to confer tissue specific, or cell-type specific expression of an attached gene. As shown in Example 5, below, SEQ ID NO: 37 confers tissue specific expression of an attached reporter gene. The expression of AP activity is much higher in the HTM cells than in HeLa or Cos cells. Thus, tissue specific promoter or 5 regulatory activity can be identified by detecting a change of expression levels from one cell type compared to another.

Expression of the rat PRL gene is highly restricted to pituitary lactotroph cells and is induced by the cAMP-dependent protein kinase A pathway. At least one of the redundant pituitary specific elements (PRL-FP111) of the proximal rat PRL promotor is required for this 10 protein kinase A effect (Rajnarayan *et al.*, *Molecular Endocrinology* 4: 502-512 (1995), herein incorporated by reference). A sequence corresponding to an upstream motif or *cis* element characteristic of PRL-FP111 is set forth in Figure 1 at residues 370-388 and 4491-4502, respectively. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or 15 concentration of molecules that bind the PRL-FP111 upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A consensus sequence (GR/PR), recognized by both the glucocorticoid receptor of rat 20 liver and the progesterone receptor from rabbit uterus, has been reported to be involved in glucocorticoid and progesterone-dependent gene expression (Von der Ahe *et al.*, *Nature* 313: 706-709 (1985), herein incorporated by reference). A sequence corresponding to a GC/PR upstream motif or *cis* element is set forth in Figure 1 at residues 433-445. In accordance with the 25 embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of glucocorticoid or progesterone or their homologues, including, but not limited to, the concentration of glucocorticoid or progesterone or their homologues bound to an GC/PR upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be 30 used in the treatment of glaucoma.

Shear stress motif (SSRE) or *cis* element has been identified in a number of genes including platelet-derived growth factor B chain, tissue plasminogen activator (tPA), ICAM-1 and TGF- $\beta$ 1 (Resnick *et al.*, *Proc. Natl. Acad. Sci. (USA)* 80: 4591-4595 (1993), herein incorporated by reference). Transcription of these genes has been associated with humoral 35 stimuli such as cytokines and bacterial products as well as hemodynamic stress forces. Sequences corresponding to a upstream shear stress motif or *cis* element are set forth in Figure 1

at residues 446-451, 1288-1293, 3597-3602, 4771-4776, and 5240-5245, respectively. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of molecules capable of binding the shear stress motif. Such agents can be used in the study of 5 glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A consensus sequence for a glucocorticoid response upstream motif (GRE) or *cis* element has been characterized (Beato, *Cell* 56: 335-344 (1989); Becker *et al.*, *Nature* 324: 686-10 688 (1986), herein incorporated by reference; Sakai *et al.*, *Genes and Development* 2: 1144-1154 (1988), herein incorporated by reference). Genes containing this upstream motif or *cis* element are regulated by glucocorticoids, progesterone, androgens and mineral corticoids (Beato, *Cell* 56: 335-344 (1989)). Sequences corresponding to glucocorticoid response upstream motif or *cis* element are set forth in Figure 1 at residues 574-600, 1042-1056, 2444-2468, 2442-2269, 3536-15 3563, 4574-4593, 4595-4614, 4851-4865, 4844-4864, 5079-5084, and 5083-5111, respectively. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of molecules capable of binding a glucocorticoid response upstream motif or *cis* element. Such 20 agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A sequence specific binding site (CBE) for the wild type nuclear phosphoprotein, p53, has been identified and appears to be associated with replication origins (Kern *et al.* *Science* 252: 25 1708-1711 (1991), herein incorporated by reference). A sequence corresponding to an CBE upstream motif or *cis* element is set forth in Figure 1 at residues 735-746. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of p53 or its homologues, including, but not limited to, the concentration of p53 or its homologues bound to an CBE upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. 30 In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

Nuclear factor ets-like (NFE), a transcriptional activator that facilitates p50 and c-Rel-dependent IgH 3' enhancer activity has been shown to bind to an NFE site in the Rel-dependent IgH 3' enhancer (Linderson *et al.*, *European J. Immunology* 27: 468-475 (1997), herein 35 incorporated by reference). A sequence corresponding to an NFE upstream motif or *cis* element is set forth in Figure 1 at residues 774-795. In accordance with the embodiments of the present

invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of nuclear factors or their homologues, including, but not limited to, the concentration of nuclear factors or their homologues bound to an NFE upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

An upstream motif or *cis* element (KTF.1-CS) for a control element 3' to the human keratin 1 gene that regulates cell type and differentiation-specific expression has been identified (Huff *et al.*, *J. Biological Chemistry* 268: 377-384 (1993), herein incorporated by reference). A sequence corresponding to an upstream motif or *cis* element characteristic of KTF.1-CS is set forth in Figure 1 at residues 843-854. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of KTF.1-CS or its homologues, including, but not limited to, the concentration of KTF.1-CS or its homologues bound to a KTF.1-CS upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A progesterone responsive element (PRE) that maps to the far upstream steroid dependent DNase hypersensitive site of chicken lysozyme chromatin has been characterized (Hecht *et al.*, *EMBO J.* 7: 2063-2073 (1988), herein incorporated by reference). The element confers hormonal regulation to a heterologous promoter and is composed of a cluster of progesterone receptor binding sites. A sequence corresponding to an upstream motif or *cis* element characteristic of PRE is set forth in Figure 1 at residues 987-1026. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of molecules capable of binding a progesterone responsive PRE upstream motif or *cis* element. Such agents may be useful in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A sequence (ETF-EGFR) has been characterized which serves as a motif for a *trans*-active transcription factor that regulates expression of the epidermal growth factor receptor (Regec *et al.*, *Blood* 85:2711-2719 (1995), herein incorporated by reference). A sequence corresponding to an ETF-EGFR upstream motif or *cis* element is set forth in Figure 1 at residues 1373-1388. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of nuclear factors or their homologues, including, but not limited to, the

concentration of nuclear factors or their homologues bound to an ETF-EGFR upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

5 A common trans-acting factor (SRE-cFos) has been shown to regulate skeletal and cardiac alpha-Actin gene transcription in muscle (Muscat *et al.*, *Molecular and Cellular Biology* 10: 4120-4133 (1988), herein incorporated by reference). A sequence corresponding to an SRE-cFos upstream motif or *cis* element is set forth in Figure 1 at residues 1447-1456. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of nuclear factors or their homologues, including, but not limited to, the concentration of nuclear factors or their homologues bound to an SRE-cFos upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

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Alu repetitive elements are unique to primates and are interspersed within the human genome with an average spacing of 4Kb. While some Alu sequences are actively transcribed by polymerase III, normal transcripts may also contain Alu-derived sequences in 5' or 3' untranslated regions (Jurka and Mikahanjaia, *J. Mol. Evolution* 32: 105-121 (1991), herein incorporated by reference, Claveria and Makalowski, *Nature* 371: 751-752 (1994), herein incorporated by reference). A sequence corresponding to an Alu upstream motif or *cis* element is set forth in Figure 1 at residues 1331-1550. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of nuclear factors or their homologues, including, but not limited to, the concentration of nuclear factors or their homologues bound to an Alu upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

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A consensus sequence for a vitellogenin gene-binding protein (VBP) upstream motif or *cis* element has been characterized (Iyer *et al.*, *Molecular and Cellular Biology* 11: 4863-4875 (1991), herein incorporated by reference). Expression of the VBP gene commences early in liver ontogeny and is not subject to circadian control. A sequence corresponding to an upstream motif or *cis* element capable of binding VBP is set forth in Figure 1 at residues 1786-1797. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of VBP or its homologues, including, but not limited to, the concentration of VBP or its homologues bound

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to an VBP upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A structural motif (Malt-CS) or *cis* element involved in the activation of all promoters of the maltose operons in *Escherichia coli* and *Klebsiella pneumoniae* has been characterized (Vidal-Inigliardi *et al.*, *J. Mol. Biol.* 218: 323-334 (1991), herein incorporated by reference). A sequence corresponding to a upstream Malt-CS motif or *cis* element is set forth in Figure 1 at residues 1832-1841. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of molecules capable of binding the upstream Malt-CS motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A consensus sequence for an estrogen receptor upstream motif or *cis* element has been characterized (ERE) (Forman *et al.*, *Mol. Endocrinology* 4: 1293-1301 (1990), herein incorporated by reference; de Verneuil *et al.*, *Nucleic Acid Res.* 18: 4489-4497 (1990), herein incorporated by reference; Gaub *et al.*, *Cell* 63: 1267-1276 (1990), herein incorporated by reference. A sequence corresponding to half an upstream motif or *cis* element capable of binding estrogen receptor is set forth in Figure 1 at residues 2166-2195, 3413-3429, and 3892-3896, respectively. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration, of the estrogen receptor or its homologues bound to an upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

Certain protein-binding sites (NF-mutagen) in Ig gene enhancers which determine transcriptional activity and inducibility have been shown to interact with nuclear factors (Lenardo *et al.*, *Science* 236: 1573-1577 (1987), herein incorporated by reference). A sequence corresponding to an NF-mutagen upstream motif or *cis* element is set forth in Figure 1 at residues 2329-2338. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of nuclear factors or their homologues, including, but not limited to, the concentration of nuclear factors or their homologues bound to an NF-mutagen upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A consensus sequence for a transcriptional repressor of c-myc (myc-PRF) upstream motif or *cis* element has been identified (Kakkis *et al.*, *Nature* 339: 718-719 (1989), herein incorporated by reference). Myc-PRF interacts with another widely distributed protein, myc-CF1 (common factor 1), which binds nearby and this association may be important in myc-PRF repression. A sequence corresponding to an upstream motif or *cis* element capable of binding myc-PRF is set forth in Figure 1 at residues 2403-2416. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of myc-PRF or its homologues, including, but not limited to, the concentration of myc-PRF or its homologues bound to an myc-PRF upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

Human transcription factor activator protein 2 (AP2) is a transcription factor that has been shown to bind to Sp1, nuclear factor 1 (NF1) and simian virus 40 transplantation (SV40 T) antigen binding sites. It is developmentally regulated (Williams and Tijan, *Gene Dev.* 5: 670-682 (1991), herein incorporated by reference; Mitchell *et al.*, *Genes Dev.* 5: 105-119 (1991), herein incorporated by reference; Coutois *et al.*, *Nucleic Acid Research* 18: 57-64 (1990), herein incorporated by reference; Comb *et al.*, *Nucleic Acid Research* 18: 3975-3982 (1990), herein incorporated by reference; Winings *et al.*, *Nucleic Acid Research* 19: 3709-3714 (1991), herein incorporated by reference). Sequences corresponding to an upstream motif or *cis* element capable of binding AP2 are set forth in Figure 1 at residues 2520-2535, and 5170-5187, respectively. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of AP2 or its homologues, including, but not limited to, the concentration of AP2 or its homologues bound to an upstream motif or *cis* element. Such agents may be useful in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

Drosophila RNA polymerase II heat shock transcription factor (HSTF) is a transcription factor that has been shown to be required for active transcription of an hsp 70 gene (Parker and Topol, *Cell* 37: 273-283 (1984), herein incorporated by reference). Sequences corresponding to an upstream motif or *cis* element capable of binding HSTF are set forth in Figure 1 at residues 2622-2635, and 5105-5132. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of HSTF or its homologues, including, but not limited to, the concentration of HSTF or its homologues bound to an HSTF upstream motif or *cis* element.

Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

5 A sequence corresponding to an upstream motif or *cis* element characteristic of SBF is set forth in Figure 1 at residues 2733-2743 (Shore *et al.*, *EMBO J.* 6: 461-467 (1987), herein incorporated by reference). In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of molecules that bind the SBF upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be 10 used in the treatment of glaucoma.

An NF1 motif or *cis* element has been identified which recognizes a family of at least six proteins (Courtois, *et al.*, *Nucleic Acid Res.* 18: 57-64 (1990), herein incorporated by reference; Mul *et al.*, *J. Virol.* 64: 5510-5518 (1990), herein incorporated by reference; Rossi *et al.*, *Cell* 52: 15 405-414 (1988), herein incorporated by reference; Gounari *et al.*, *EMBO J.* 10: 559-566 (1990), herein incorporated by reference; Goyal *et al.*, *Mol. Cell Biol.* 10: 1041-1048 (1990); herein incorporated by reference; Mermond *et al.*, *Nature* 332: 557-561 (1988), herein incorporated by reference; Gronostajski *et al.*, *Molecular and Cellular Biology* 5: 964-971 (1985), herein incorporated by reference; Hennighausen *et al.*, *EMBO J.* 5: 1367-1371 (1986), herein incorporated by reference; Chodosh *et al.*, *Cell* 53: 11-24 (1988), herein incorporated by 20 reference). The NF1 protein will bind to an NF1 motif or *cis* element either as a dimer (if the motif is palindromic) or as a single molecule (if the motif is not palindromic). The NF1 protein is induced by TGF $\beta$  (Faisst and Meyer, *Nucleic Acid Research* 20: 3-26 (1992), herein incorporated by reference). Sequences corresponding to an upstream motif or *cis* element capable of binding NF1 are set forth in Figure 1 at residues 2923-2938, 4143-4167, and 4886-25 4900, respectively. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of NF1 or its homologues, including, but not limited to, the concentration of NF1 or its homologues bound to an upstream motif or *cis* element. Such agents can be used in the 30 study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

35 Conserved regulatory sequences (NF-MHCIIA/B) of a rabbit major histocompatibility complex (MHC) class II gene are responsible for binding two distinct nuclear factors NF-MHCIIA and NF-MHCIIB and are believed to be involved in the regulation of coordinate expression of the class II genes -- eg. MHC class II gene in B lymphocytes (Sittisombut

Molecular and Cellular Biology 5: 2034-2041 (1988), herein incorporated by reference). A sequence corresponding to an NF-MHCIIA/B upstream motif or *cis* element is set forth in Figure 1 at residues 2936-2944. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of NF-MHCIIA or NF-MHCIIIB or their homologues, including, but not limited to, the concentration of NF-MHCIIA or NF-MHCIIIB or their homologues bound to an NF-MHCIIA/B upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

10 PEA 1 binding motifs or *cis* elements have been identified (Piette and Yaniv, EMBO J. 5: 1331-1337 (1987), herein incorporated by reference). The PEA1 protein is a transcription factor that is reported to bind to both the polyoma virus and *c-fos* enhancers. A sequence corresponding to an upstream motif or *cis* element capable of binding PEA1 is set forth in Figure 1 at residues 3285-3298. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of PEA1 or its homologues, including, but not limited to, the concentration of PEA1 or its homologues bound to an upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

15 A conserved *cis*-acting regulatory element (ICS) has been shown to bind trans-acting constitutive nuclear factors present in lymphocytes and fibroblasts which are involved in the interferon (IFN)-mediated transcriptional enhancement of MHC class I and other genes (Shirayoshi *et al.*, Proc. Natl. Acad. Sci. (USA) 85: 5884-5888 (1988), herein incorporated by reference). A sequence corresponding to an ICS upstream motif or *cis* element is set forth in Figure 1 at residues 3688-3699. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of nuclear factors or their homologues, including, but not limited to, the concentration of nuclear factors or their homologues bound to an ICS upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

20 30 35 A consensus sequence for an ISGF2 upstream motif or *cis* element has been characterized (Iman *et al.*, Nucleic Acids Res. 18: 6573-6580 (1990), herein incorporated by reference; Harada *et al.*, Cell 63: 303-312 (1990), herein incorporated by reference; Yu-Lee *et al.*, Mol. Cell Biol.

10: 3087-3094 (1990), herein incorporated by reference; Pine *et al.*, *Mol. Cell Biol.* 10: 32448-2457 (1990), herein incorporated by reference). ISGF2 is induced by interferon  $\alpha$  and  $\gamma$ , prolactin and virus infections. A sequence corresponding to an upstream motif or *cis* element capable of binding ISGF2 is set forth in Figure 1 at residues 4170-4179. In accordance with the 5 embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of ISGF2 or its homologues, including, but not limited to, the concentration of ISGF2 or its homologues bound to an upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another 10 embodiment such agents can be used in the treatment of glaucoma.

A sequence corresponding to an upstream motif or *cis* element capable of binding zinc is set forth in Figure 1 at residues 4285-4292. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of zinc. Such agents can be used in the study of 15 glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A sequence corresponding to an upstream motif or *cis* element characteristic of CAP/CRP-galO is set forth in Figure 1 at residues 4379-4404 (Taniguchi *et al.*, *Proc. Natl. Acad. Sci. (USA)* 76: 5090-5094 (1979), herein incorporated by reference). In accordance with the 20 embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of molecules that bind the CAP/CRP-galO upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of 25 glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

Human transcription factor activator protein 1 (AP1) is a transcription factor that has been shown to regulate genes which are highly expressed in transformed cells such as stromelysin, *c-fos*,  $\alpha_1$ -anti-trypsin and collagenase (Gutman and Waslyk, *EMBO J.* 9.7: 2241-30 2246 (1990), herein incorporated by reference; Martin *et al.*, *Proc. Natl. Acad. Sci. USA* 85: 5839-5843 (1988), herein incorporated by reference; Jones *et al.*, *Genes and Development* 2: 267-281 (1988), herein incorporated by reference; Faisst and Meyer, *Nucleic Acid Research* 20: 3-26 (1992), herein incorporated by reference; Kim *et al.*, *Molecular and Cellular Biology* 10: 1492-1497 (1990), herein incorporated by reference; Baumhueter *et al.*, *EMBO J.* 7: 2485-2493 35 (1988), herein incorporated by reference). The AP1 transcription factor has been associated with genes that are activated by 12-O-tetradecanoylphorbol-13-acetate (TPA) (Gutman and Waslyk,

*EMBO J.* 7: 2241-2246 (1990)). Sequences corresponding to an upstream motif or *cis* element capable of binding AP1 are set forth in Figure 1 at residues 4428-4434 and 4627-4639, respectively. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of AP1 or its homologues, including, but not limited to, the concentration of AP1 or its homologues bound to an upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

The sex-determining region of the Y chromosome gene, *sry*, is expressed in the fetal mouse for a brief period, just prior to testis differentiation. SRY is a DNA binding protein known to bind to a CACA-rich region in the *sry* gene (Vriz *et al.*, *Biochemistry and Molecular Biology International* 37: 1137-1146 (1995), herein incorporated by reference). A sequence corresponding to an upstream motif or *cis* element capable of binding SRY is set forth in Figure 1 at residues 4625-4634. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of SRY or its homologues, including, but not limited to, the concentration of SRY or its homologues bound to an upstream motif or *cis* element. Such agents may be useful in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A sequence corresponding to an upstream motif or *cis* element characteristic of GC2-GH is set forth in Figure 1 at residues 4689-4711 (West *et al.*, *Molecular and Cellular Biology* 7: 1193-1197 (1987), herein incorporated by reference). In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of GC2-GH or its homologues, including, but not limited to, the concentration of GC2-GH or its homologues bound to an upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

PEA 3 binding motifs or *cis* elements have been identified (Martin *et al.*, *Proc. Natl. Acad. Sci. (USA)* 85: 5839-5843 (1988), herein incorporated by reference; Gutman and Waslylyk, *EMBO J.* 7: 2241-2246 (1990), herein incorporated by reference). The PEA3 protein is a transcription factor that is reported to interact with AP1 like proteins (Martin *et al.*, *Proc. Natl. Acad. Sci. (USA)* 85: 5839-5843 (1988), herein incorporated by reference). Sequences corresponding to an upstream motif or *cis* element capable of binding PEA3 is set forth in Figure

1 at residues 4765-4769. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of PEA3 or its homologues, including, but not limited to, the concentration of PEA3 or its homologues bound to an upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

5 Mammalian interspersed repetitive (MIR) is an element involved in the coding and processing sequences of mammalian genes. The MIR element is at least 260 bp in length and numbers about  $10^5$  copies within the mammalian genome (Murnane *et al.*, *Nucleic Acids Research* 15: 2837-2839 (1995), herein incorporated by reference). A sequence corresponding to 10 an MIR upstream motif or *cis* element is set forth in Figure 1 at residues 4759-4954. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of nuclear factors or their homologues, including, but not limited to, the concentration of nuclear factors or 15 their homologues bound to an MIR upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

20 Normal liver and differentiated hepatoma cell lines contain a hepatocyte-specific nuclear factor (HNF-1) which binds *cis*-acting element sequences within the promoters of the alpha and beta chains of fibrinogen and alpha 1-antitrypsin (Baumhueter *et al.*, *EMBO J.* 8: 2485-2493, herein incorporated by reference). A sequence corresponding to an HNF-1 upstream motif or *cis* element is set forth in Figure 1 at residues 4923-4941. In accordance with the embodiments of 25 the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of HNF-1 or its homologues, including, but not limited to, the concentration of HNF-1 or its homologues bound to an HNF-1 upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another 30 embodiment such agents can be used in the treatment of glaucoma.

A number of *cis* elements or upstream motifs have been associated with gene regulation by steroid and thyroid hormones (e.g. glucocorticoid and estrogen)(Beato, *Cell* 56: 335-344 (1989), herein incorporated by reference; Brent *et al.*, *Molecular Endocrinology* 89:1996-2000 (1989), herein incorporated by reference; Glass *et al.*, *Cell* 54: 313-323 (1988), herein 35 incorporated by reference; Evans, *Science* 240: 889-895 (1988), herein incorporated by reference).

A consensus sequence for a thyroid receptor upstream motif or *cis* element (TRE) has been characterized (Beato, *Cell* 56: 335-344 (1989), herein incorporated by reference). A sequence corresponding to a thyroid receptor upstream motif or *cis* element is set forth in Figure 1 at residues 5151-5156. Thyroid hormones are capable of regulating genes containing a thyroid receptor upstream motif or *cis* element (Glass *et al.*, *Cell* 54: 313-323 (1988), herein incorporated by reference). Thyroid hormones can negatively regulate TIGR. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of molecules capable of binding a thyroid receptor upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

NF $\kappa$ B is a transcription factor that is reportedly associated with a number of biological processes including T-cell activation and cytokine regulation (Lenardo *et al.*, *Cell* 58: 227-229 (1989), herein incorporated by reference). A consensus upstream motif or *cis* element capable of binding NF $\kappa$ B has been reported (Lenardo *et al.*, *Cell* 58: 227-229 (1989)). Sequences corresponding to an upstream motif or *cis* element capable of binding NF $\kappa$ B are set forth in Figure 1 at residues 5166-5175. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of NF $\kappa$ B or its homologues, including, but not limited to, the concentration of NF $\kappa$ B or its homologues bound to an upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

25 Illustrative Uses of the Nucleic Acids of the Invention

Where one or more of the agents is a nucleic acid molecule, such nucleic acid molecule may be sense, antisense or triplex oligonucleotides corresponding to any part of the TIGR promoter, TIGR cDNA, TIGR intron, TIGR exon or TIGR gene. In some embodiments these nucleic acids may be about 20 bases in length, as for example, SEQ. ID NO: 6-25 or 33. In some circumstances, the nucleic acids may be only about 8 bases in length. Short nucleic acids may be particularly useful in hybridization to immobilized nucleic acids in order to determine the presence of specific sequences, such as by the known methods of sequencing by hybridization.

The TIGR promoter, or fragment thereof, of the present invention may be cloned into a suitable vector and utilized to promote the expression of a marker gene (e.g. firefly luciferase (de

Wet, *Mol. Cell Biol.* 7: 725-737 (1987), herein incorporated by reference) or GUS (Jefferson *et al.*, *EMBO J.* 6: 3901-3907 (1987), herein incorporated by reference)).

In another embodiment of the present invention, a TIGR promoter may be cloned into a suitable vector and utilized to promote the expression of a TIGR gene in a suitable eukaryotic or 5 prokaryotic host cell (e.g. human trabecular cell, chinese hamster cell, *E. coli*). In another embodiment of the present invention, a TIGR promoter may be cloned into a suitable vector and utilized to promote the expression of a homologous or heterologous gene in a suitable eukaryotic or prokaryotic host cells (e.g. human trabecular cell lines, chinese hamster cells, *E. coli*).

Similarly, the TIGR promoter, regions of the TIGR 5' regulatory region from about 10 bp to about 1.6 kb, or regions of the TIGR 5' regulatory region that confer tissue specific expression can be used in DNA constructs, vectors, and cells to express an operably linked gene. For example, these TIGR sequences can control expression of a linked gene in a vector used for producing transgenic animals. In this way, cells or animals can be produced that express a gene in a tissue specific manner. One embodiment involves a gene therapy approach to treating 15 glaucoma or IOP-disorder, where a transgene having the TIGR 5'regulatory sequence is used to direct expression of a therapeutic gene into the trabecular meshwork or the cells of the trabecular meshwork. Experimental animal models can also be produced using the transgenic technology. These animal models, or cells from them or comprising these TIGR sequences, can be used in methods to screen for compounds that modulate expression of TIGR, and especially compounds 20 that affect the steroid regulation of TIGR expression. These methods will produce therapeutic or diagnostic agents, which agents are specifically included in the invention.

Thus, transgenic animals having an introduced DNA that comprises at least a portion of the TIGR 5' regulatory region are specifically included in this invention. Preferred embodiments have 5' regulatory sequences of SEQ ID NO: 37 or 38, or variant thereof, or a region of SEQ ID 25 NO: 3 or 34, especially those that confer tissue specific expression. One skilled in the art is familiar with the production of transgenic construct, vectors, and animals (*See, Ausubel et al., Current Protocols in Molecular Biology*).

In addition, as noted above, the 5' regulatory regions can be used to screen and identify 30 DNA binding proteins. The specific binding of proteins or cellular components to the 5' regulatory regions can be detected, see Example 5. Screening methods for compounds that modulate the binding can also be produced using the 5'regulatory regions of the invention, or vectors or cells comprising those regions. DNA binding proteins that increase or decrease expression can be identified. For example, cells that do not show native expression of TIGR, such as HeLa cells, may possess proteins or cellular components that inhibit expression of TIGR. 35 While cells like TM cells may possess DNA binding proteins or cellular components that allow expression of TIGR or increase the level of TIGR expression in response to other agents, such as

steroids or dexamethasone. Thus, the invention encompasses a number of methods to detect and identify proteins or cellular components that modulate expression of TIGR, or the expression of a gene under the control of the TIGR 5' regulatory region. Also, methods to detect compounds that effect that modulation are similarly encompassed, as well as therapeutic and diagnostic agents that are identified from those methods.

Practitioners are familiar with the standard resource materials which describe specific conditions and procedures for the construction, manipulation and isolation of macromolecules (e.g., DNA molecules, plasmids, etc.), generation of recombinant organisms and the screening and isolating of clones, (see for example, Sambrook *et al.*, In *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press (1989), herein incorporated by reference in its entirety; Old and Primrose, In *Principles of Gene Manipulation: An Introduction To Genetic Engineering*, Blackwell (1994), herein incorporated by reference).

The TIGR promoter, or any portion thereof, or an about 10 to about 500 bases fragment thereof, of the present invention may be used in a gel-retardation or band shift assay (Old and Primrose, In *Principles of Gene Manipulation: An Introduction To Genetic Engineering*, Blackwell (1994)). Nucleic acids or fragments comprising any of the *cis* elements identified in the present invention may be used in a gel-retardation or band shift assay to isolate proteins capable of binding the *cis* element. Suitable DNA fragments or molecules comprise or consist of one or more of the following: sequences corresponding to an upstream motif or *cis* element characteristic of PRL-FP111 as set forth in Figure 1 at residues 370-388, and 4491-4502, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding GR/PR as set forth in Figure 1 at residues 433-445, sequences corresponding to an upstream shear stress motif or *cis* element as set forth in Figure 1 at residues 446-451, 1288-1293, 3597-3602, 4771-4776, and 5240-5245, respectively, sequences corresponding to glucocorticoid response upstream motif or *cis* element as set forth in Figure 1 at residues 574-600, 1042-1056, 2444-2468, 2442-2269, 3536-3563, 4574-4593, 4595-4614, 4851-4865, 4844-4864, 5079-5084, 5083-5111, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding CBE as set forth in Figure 1 at residues 735-746, a sequence corresponding to an upstream motif or *cis* element capable of binding NFE as set forth in Figure 1 at residues 774-795, a sequence corresponding to an upstream motif or *cis* element capable of binding KTF.1-CS as set forth in Figure 1 at residues 843-854, a sequence corresponding to an upstream motif or *cis* element capable of binding PRE is set forth in Figure 1 at residues 987-1026, a sequence corresponding to an upstream motif or *cis* element capable of binding ETF-EGFR as set forth in Figure 1 at residues 1373-1388, a sequence corresponding to an upstream motif or *cis* element capable of binding SRE-cFos as set forth in Figure 1 at residues 1447-1456, a sequence corresponding to an upstream motif or *cis* element capable of binding Alu as set forth in Figure

1 at residues 1331-1550, a sequence corresponding to an upstream motif or *cis* element capable  
of binding VBP as set forth in Figure 1 at residues 1786-1797, a sequence corresponding to an  
upstream motif or *cis* element capable of binding Malt-CS as set forth in Figure 1 at residues  
1832-1841, sequences corresponding to an upstream motif or *cis* element capable of binding  
5 ERE as set forth in Figure 1 at residues 2167-2195, 3413-3429, and 3892-3896, respectively, a  
sequence corresponding to an upstream motif or *cis* element capable of binding NF-mutagen as  
set forth in Figure 1 at residues 2329-2338, a sequence corresponding to an upstream motif or *cis*  
10 element capable of binding myc-PRF as set forth in Figure 1 at residues 2403-2416, sequences  
corresponding to an upstream motif or *cis* element capable of binding AP2 as set forth in Figure  
1 at residues 2520-2535 and 5170-5187, respectively, sequences corresponding to an upstream  
motif or *cis* element capable of binding HSTF as set forth in Figure 1 at residues 2622-2635, and  
15 5105-5132, respectively, a sequence corresponding to an upstream motif or *cis* element  
characteristic of SBF as set forth in Figure 1 at residues 2733-2743, sequences corresponding to  
an upstream motif or *cis* element capable of binding NF-1 as set forth in Figure 1 at residues  
2923-2938, 4144-4157, and 4887-4900, respectively, a sequence corresponding to an upstream  
motif or *cis* element capable of binding NF-MHCIIA/B as set forth in Figure 1 at residues 2936-  
2944, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA1 as  
set forth in Figure 1 at residues 3285-3298, a sequence corresponding to an upstream motif or *cis*  
20 element capable of binding ICS as set forth in Figure 1 at residues 3688-3699, a sequence  
corresponding to an upstream motif or *cis* element capable of binding ISGF2 as set forth in  
Figure 1 at residues 4170-4179, a sequence corresponding to an upstream motif or *cis* element  
capable of binding zinc as set forth in Figure 1 at residues 4285-4293, a sequence corresponding  
to an upstream motif or *cis* element characteristic of CAP/CRP-galO as set forth in Figure 1 at  
25 residues 4379-4404, sequences corresponding to an upstream motif or *cis* element capable of  
binding AP1 as set forth in Figure 1 at residues 4428-4434, and 4627-4639, respectively, a  
sequence corresponding to an upstream motif or *cis* element capable of binding SRY as set forth  
in Figure 1 at residues 4625-4634, a sequence corresponding to an upstream motif or *cis* element  
characteristic of GC2 as set forth in Figure 1 at residues 4678-4711, a sequence corresponding to  
an upstream motif or *cis* element capable of binding PEA3 as set forth in Figure 1 at residues  
30 4765-4769, a sequence corresponding to an upstream motif or *cis* element capable of MIR as set  
forth in Figure 1 at residues 4759-4954, a sequence corresponding to an upstream motif or *cis*  
element capable of binding NF-HNF-1 as set forth in Figure 1 at residues 4923-4941, a sequence  
corresponding to a thyroid receptor upstream motif or *cis* element as set forth in Figure 1 at  
35 residues 5151-5156, and a sequence corresponding to an upstream motif or *cis* element capable  
of binding NF $\kappa$ B as set forth in Figure 1 at residues 5166-5175.

A preferred class of agents of the present invention comprises nucleic acid molecules encompassing all or a fragment of the "TIGR promoter" or 5' flanking gene sequences. As used herein, the terms "TIGR promoter" or "promoter" is used in an expansive sense to refer to the regulatory sequence(s) that control mRNA production. Thus, TIGR promoter sequences can be identified by those sequences that functionally effect the initiation, rate, or amount of transcription of the TIGR gene product mRNA. Such sequences include RNA polymerase binding sites, glucocorticoid response elements, enhancers, etc. These sequences may preferably be found within the specifically disclosed 5' upstream region sequences disclosed here, and most preferably within an about 500 base region 5' to the start of transcription or within an about 300 base region 5' of the transcription start site. However, other genomic sequences may be a TIGR promoter. Methods known in the art to identify distant promoter elements can be used with the disclosed sequences and nucleic acids to identify and define these distant TIGR promoter sequences. Such TIGR molecules may be used to diagnose the presence of glaucoma and the severity of or susceptibility to glaucoma. Such molecules may be either DNA or RNA.

A functional regulatory region of the TIGR gene may be a TIGR promoter sequence. It may also include transcription enhancer sites and transcription inhibitor sites or binding sites for a number of known proteins or molecules demonstrated as effecting transcription. A number of regulatory elements are discussed below, and the equivalent of those activities can represent the functional regulatory region of the TIGR gene. The methods for identifying and detecting the activity and function of these regulatory regions are known in the art.

Fragment nucleic acid molecules may encode significant portion(s) of, or indeed most of, SEQ ID NO: 1 or SEQ ID NO: 3 or SEQ ID NO: 4 or SEQ ID NO: 5. Alternatively, the fragments may comprise smaller oligonucleotides (having from about 15 to about 250 nucleotide residues, and more preferably, about 15 to about 30 nucleotide residues.). Such oligonucleotides include SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25.

Alternatively such oligonucleotides may derive from either the TIGR promoter, TIGR introns, TIGR exons, TIGR cDNA and TIGR downstream sequences comprise or consist of one or more of the following: sequences corresponding to an upstream motif or *cis* element characteristic of PRL-FP111 as set forth in Figure 1 at residues 370-388, and 4491-4502, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding GR/PR as set forth in Figure 1 at residues 433-445, sequences corresponding to an upstream shear stress motif or *cis* element as set forth in Figure 1 at residues 446-451, 1288-1293, 3597-3602, 4771-4776, and 5240-5245, respectively, sequences corresponding to glucocorticoid

response upstream motif or *cis* element as set forth in Figure 1 at residues 574-600, 1042-1056, 2444-2468, 2442-2269, 3536-3563, 4574-4593, 4595-4614, 4851-4865, 4844-4864, 5079-5084, 5083-5111, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding CBE as set forth in Figure 1 at residues 735-746, a sequence corresponding to an upstream motif or *cis* element capable of binding NFE as set forth in Figure 1 at residues 774-795, a sequence corresponding to an upstream motif or *cis* element capable of binding KTF-1-CS as set forth in Figure 1 at residues 843-854, a sequence corresponding to an upstream motif or *cis* element capable of binding PRE is set forth in Figure 1 at residues 987-1026, a sequence corresponding to an upstream motif or *cis* element capable of binding ETF-EGFR as set forth in Figure 1 at residues 1373-1388, a sequence corresponding to an upstream motif or *cis* element capable of binding SRE-cFos as set forth in Figure 1 at residues 1447-1456, a sequence corresponding to an upstream motif or *cis* element capable of binding Alu as set forth in Figure 1 at residues 1331-1550, a sequence corresponding to an upstream motif or *cis* element capable of binding VBP as set forth in Figure 1 at residues 1786-1797, a sequence corresponding to an upstream motif or *cis* element capable of binding Malt-CS as set forth in Figure 1 at residues 1832-1841, sequences corresponding to an upstream motif or *cis* element capable of binding ERE as set forth in Figure 1 at residues 2167-2195, 3413-3429, and 3892-3896, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-mutagen as set forth in Figure 1 at residues 2329-2338, a sequence corresponding to an upstream motif or *cis* element capable of binding myc-PRF as set forth in Figure 1 at residues 2403-2416, sequences corresponding to an upstream motif or *cis* element capable of binding AP2 as set forth in Figure 1 at residues 2520-2535 and 5170-5187, respectively, sequences corresponding to an upstream motif or *cis* element capable of binding HSTF as set forth in Figure 1 at residues 2622-2635, and 5105-5132, respectively, a sequence corresponding to an upstream motif or *cis* element characteristic of SBF as set forth in Figure 1 at residues 2733-2743, sequences corresponding to an upstream motif or *cis* element capable of binding NF-1 as set forth in Figure 1 at residues 2923-2938, 4144-4157, and 4887-4900, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-MHCIIA/B as set forth in Figure 1 at residues 2936-2944, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA1 as set forth in Figure 1 at residues 3285-3298, a sequence corresponding to an upstream motif or *cis* element capable of binding ICS as set forth in Figure 1 at residues 3688-3699, a sequence corresponding to an upstream motif or *cis* element capable of binding ISGF2 as set forth in Figure 1 at residues 4170-4179, a sequence corresponding to an upstream motif or *cis* element capable of binding zinc as set forth in Figure 1 at residues 4285-4293, a sequence corresponding to an upstream motif or *cis* element characteristic of CAP/CRP-galO as set forth in Figure 1 at residues 4379-4404, sequences corresponding to an upstream motif or *cis* element capable of

binding AP1 as set forth in Figure 1 at residues 4428-4434, and 4627-4639, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding SRY as set forth in Figure 1 at residues 4625-4634, a sequence corresponding to an upstream motif or *cis* element characteristic of GC2 as set forth in Figure 1 at residues 4678-4711, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA3 as set forth in Figure 1 at residues 4765-4769, a sequence corresponding to an upstream motif or *cis* element capable of MIR as set forth in Figure 1 at residues 4759-4954, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-HNF-1 as set forth in Figure 1 at residues 4923-4941, a sequence corresponding to a thyroid receptor upstream motif or *cis* element as set forth in Figure 1 at residues 5151-5156, and a sequence corresponding to an upstream motif or *cis* element capable of binding NF $\kappa$ B as set forth in Figure 1 at residues 5166-5175. For such purpose, the oligonucleotides must be capable of specifically hybridizing to a nucleic acid molecule genetically or physically linked to the TIGR gene. As used herein, the term "linked" refers to genetically, physically or operably linked.

As used herein, two nucleic acid molecules are said to be capable of specifically hybridizing to one another if the two molecules are capable of forming an anti-parallel, double-stranded nucleic acid structure, whereas they are unable to form a double-stranded structure when incubated with a non-TIGR nucleic acid molecule. A nucleic acid molecule is said to be the "complement" of another nucleic acid molecule if they exhibit complete complementarity. As used herein, molecules are said to exhibit "complete complementarity" when every nucleotide of one of the molecules is complementary to a nucleotide of the other. Two molecules are said to be "minimally complementary" if they can hybridize to one another with sufficient stability to permit them to remain annealed to one another under at least conventional "low-stringency" conditions. Similarly, the molecules are said to be "complementary" if they can hybridize to one another with sufficient stability to permit them to remain annealed to one another under conventional "high-stringency" conditions. Conventional stringency conditions are described by Sambrook, J., et al., (In: *Molecular Cloning, a Laboratory Manual*, 2nd Edition, Cold Spring Harbor Press, Cold Spring Harbor, New York (1989)), and by Haymes, B.D., et al. (In: *Nucleic Acid Hybridization, A Practical Approach*, IRL Press, Washington, DC (1985)), both herein incorporated by reference). Departures from complete complementarity are therefore permissible, as long as such departures do not completely preclude the capacity of the molecules to form a double-stranded structure. Thus, in order for an oligonucleotide to serve as a primer it need only be sufficiently complementary in sequence to be able to form a stable double-stranded structure under the particular solvent and salt concentrations employed.

Apart from their diagnostic or prognostic uses, such oligonucleotides may be employed to obtain other TIGR nucleic acid molecules. Such molecules include the TIGR-encoding nucleic

acid molecule of non-human animals (particularly, cats, monkeys, rodents and dogs), fragments thereof, as well as their promoters and flanking sequences. Such molecules can be readily obtained by using the above-described primers to screen cDNA or genomic libraries obtained from non-human species. Methods for forming such libraries are well known in the art. Such 5 analogs may differ in their nucleotide sequences from that of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, or 10 from molecules consisting of sequences corresponding to an upstream motif or *cis* element characteristic of PRL-FP111 as set forth in Figure 1 at residues 370-388, and 4491-4502, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding GR/PR as set forth in Figure 1 at residues 433-445, sequences corresponding to an upstream shear stress motif or *cis* element as set forth in Figure 1 at residues 446-451, 1288-1293, 3597- 15 3602, 4771-4776, and 5240-5245, respectively, sequences corresponding to glucocorticoid response upstream motif or *cis* element as set forth in Figure 1 at residues 574-600, 1042-1056, 2444-2468, 2442-2269, 3536-3563, 4574-4593, 4595-4614, 4851-4865, 4844-4864, 5079-5084, 5083-5111, respectively, a sequence corresponding to an upstream motif or *cis* element capable 20 of binding CBE as set forth in Figure 1 at residues 735-746, a sequence corresponding to an upstream motif or *cis* element capable of binding NFE as set forth in Figure 1 at residues 774- 795, a sequence corresponding to an upstream motif or *cis* element capable of binding KTF.1-CS as set forth in Figure 1 at residues 843-854, a sequence corresponding to an upstream motif or 25 *cis* element capable of binding PRE is set forth in Figure 1 at residues 987-1026, a sequence corresponding to an upstream motif or *cis* element capable of binding ETF-EGFR as set forth in Figure 1 at residues 1373-1388, a sequence corresponding to an upstream motif or *cis* element 30 capable of binding SRE-cFos as set forth in Figure 1 at residues 1447-1456, a sequence corresponding to an upstream motif or *cis* element capable of binding Alu as set forth in Figure 1 at residues 1331-1550, a sequence corresponding to an upstream motif or *cis* element capable of binding VBP as set forth in Figure 1 at residues 1786-1797, a sequence corresponding to an upstream motif or *cis* element capable of binding Malt-CS as set forth in Figure 1 at residues 35 1832-1841, sequences corresponding to an upstream motif or *cis* element capable of binding ERE as set forth in Figure 1 at residues 2167-2195, 3413-3429, and 3892-3896, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-mutagen as set forth in Figure 1 at residues 2329-2338, a sequence corresponding to an upstream motif or *cis* element capable of binding myc-PRF as set forth in Figure 1 at residues 2403-2416, sequences corresponding to an upstream motif or *cis* element capable of binding AP2 as set forth in Figure

1 at residues 2520-2535 and 5170-5187, respectively, sequences corresponding to an upstream motif or *cis* element capable of binding HSTF as set forth in Figure 1 at residues 2622-2635, and 5105-5132, respectively, a sequence corresponding to an upstream motif or *cis* element characteristic of SBF as set forth in Figure 1 at residues 2733-2743, sequences corresponding to an upstream motif or *cis* element capable of binding NF-1 as set forth in Figure 1 at residues 2923-2938, 4144-4157, and 4887-4900, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-MHCIIA/B as set forth in Figure 1 at residues 2936-2944, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA1 as set forth in Figure 1 at residues 3285-3298, a sequence corresponding to an upstream motif or *cis* element capable of binding ICS as set forth in Figure 1 at residues 3688-3699, a sequence corresponding to an upstream motif or *cis* element capable of binding ISGF2 as set forth in Figure 1 at residues 4170-4179, a sequence corresponding to an upstream motif or *cis* element capable of binding zinc as set forth in Figure 1 at residues 4285-4293, a sequence corresponding to an upstream motif or *cis* element characteristic of CAP/CRP-galO as set forth in Figure 1 at residues 4379-4404, sequences corresponding to an upstream motif or *cis* element capable of binding AP1 as set forth in Figure 1 at residues 4428-4434, and 4627-4639, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding SRY as set forth in Figure 1 at residues 4625-4634, a sequence corresponding to an upstream motif or *cis* element characteristic of GC2 as set forth in Figure 1 at residues 4678-4711, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA3 as set forth in Figure 1 at residues 4765-4769, a sequence corresponding to an upstream motif or *cis* element capable of MIR as set forth in Figure 1 at residues 4759-4954, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-HNF-1 as set forth in Figure 1 at residues 4923-4941, a sequence corresponding to a thyroid receptor upstream motif or *cis* element as set forth in Figure 1 at residues 5151-5156, and a sequence corresponding to an upstream motif or *cis* element capable of binding NF $\kappa$ B as set forth in Figure 1 at residues 5166-5175 because complete complementarity is not needed for stable hybridization. The TIGR nucleic acid molecules of the present invention therefore also include molecules that, although capable of specifically hybridizing with TIGR nucleic acid molecules may lack "complete complementarity."

30 Any of a variety of methods may be used to obtain the above-described nucleic acid molecules (Elles, Methods in Molecular Medicine: Molecular Diagnosis of Genetic Diseases, Humana Press (1996), herein incorporated by reference). SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25,

SEQ ID NO: 33, sequences corresponding to an upstream motif or *cis* element characteristic of PRL-FP111 as set forth in Figure 1 at residues 370-388, and 4491-4502, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding GR/PR as set forth in Figure 1 at residues 433-445, sequences corresponding to an upstream shear stress motif or *cis* element as set forth in Figure 1 at residues 446-451, 1288-1293, 3597-3602, 4771-4776, and 5 5240-5245, respectively, sequences corresponding to glucocorticoid response upstream motif or *cis* element as set forth in Figure 1 at residues 574-600, 1042-1056, 2444-2468, 2442-2269, 3536-3563, 4574-4593, 4595-4614, 4851-4865, 4844-4864, 5079-5084, 5083-5111, respectively, 10 a sequence corresponding to an upstream motif or *cis* element capable of binding CBE as set forth in Figure 1 at residues 735-746, a sequence corresponding to an upstream motif or *cis* element capable of binding NFE as set forth in Figure 1 at residues 774-795, a sequence corresponding to an upstream motif or *cis* element capable of binding KTF.1-CS as set forth in Figure 1 at residues 843-854, a sequence corresponding to an upstream motif or *cis* element capable of binding PRE is set forth in Figure 1 at residues 987-1026, a sequence corresponding to 15 an upstream motif or *cis* element capable of binding ETF-EGFR as set forth in Figure 1 at residues 1373-1388, a sequence corresponding to an upstream motif or *cis* element capable of binding SRE-cFos as set forth in Figure 1 at residues 1447-1456, a sequence corresponding to an upstream motif or *cis* element capable of binding Alu as set forth in Figure 1 at residues 1331- 1550, a sequence corresponding to an upstream motif or *cis* element capable of binding VBP as 20 set forth in Figure 1 at residues 1786-1797, a sequence corresponding to an upstream motif or *cis* element capable of binding Malt-CS as set forth in Figure 1 at residues 1832-1841, sequences corresponding to an upstream motif or *cis* element capable of binding ERE as set forth in Figure 1 at residues 2167-2195, 3413-3429, and 3892-3896, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-mutagen as set forth in Figure 1 at 25 residues 2329-2338, a sequence corresponding to an upstream motif or *cis* element capable of binding myc-PRF as set forth in Figure 1 at residues 2403-2416, sequences corresponding to an upstream motif or *cis* element capable of binding AP2 as set forth in Figure 1 at residues 2520- 2535 and 5170-5187, respectively, sequences corresponding to an upstream motif or *cis* element capable of binding HSTF as set forth in Figure 1 at residues 2622-2635, and 5105-5132, 30 respectively, a sequence corresponding to an upstream motif or *cis* element characteristic of SBF as set forth in Figure 1 at residues 2733-2743, sequences corresponding to an upstream motif or *cis* element capable of binding NF-1 as set forth in Figure 1 at residues 2923-2938, 4144-4157, and 4887-4900, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-MHCIIA/B as set forth in Figure 1 at residues 2936-2944, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA1 as set forth in 35 Figure 1 at residues 3285-3298, a sequence corresponding to an upstream motif or *cis* element

capable of binding ICS as set forth in Figure 1 at residues 3688-3699, a sequence corresponding to an upstream motif or *cis* element capable of binding ISGF2 as set forth in Figure 1 at residues 4170-4179, a sequence corresponding to an upstream motif or *cis* element capable of binding zinc as set forth in Figure 1 at residues 4285-4293, a sequence corresponding to an upstream motif or *cis* element characteristic of CAP/CRP-galO as set forth in Figure 1 at residues 4379-4404, sequences corresponding to an upstream motif or *cis* element capable of binding AP1 as set forth in Figure 1 at residues 4428-4434, and 4627-4639, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding SRY as set forth in Figure 1 at residues 4625-4634, a sequence corresponding to an upstream motif or *cis* element characteristic of GC2 as set forth in Figure 1 at residues 4678-4711, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA3 as set forth in Figure 1 at residues 4765-4769, a sequence corresponding to an upstream motif or *cis* element capable of MIR as set forth in Figure 1 at residues 4759-4954, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-HNF-1 as set forth in Figure 1 at residues 4923-4941, a sequence corresponding to a thyroid receptor upstream motif or *cis* element as set forth in Figure 1 at residues 5151-5156, and a sequence corresponding to an upstream motif or *cis* element capable of binding NF $\kappa$ B as set forth in Figure 1 at residues 5166-5175 may be used to synthesize all or any portion of the TIGR promoter or any of the TIGR upstream motifs or portions the TIGR cDNA (Zamechik *et al.*, Proc. Natl. Acad. Sci. (U.S.A.) 83:4143 (1986); Goodchild *et al.*, Proc. Natl. Acad. Sci. (U.S.A.) 85:5507 (1988); Wickstrom *et al.*, Proc. Natl. Acad. Sci. (U.S.A.) 85:1028; Holt, J.T. *et al.*, Molec. Cell. Biol. 8:963 (1988); Gerwirtz, A.M. *et al.*, Science 242:1303 (1988); Anfossi, G., *et al.*, Proc. Natl. Acad. Sci. (U.S.A.) 86:3379 (1989); Becker, D., *et al.*, EMBO J. 8:3679 (1989); all of which references are incorporated herein by reference).

Automated nucleic acid synthesizers may be employed for this purpose. In lieu of such synthesis, the disclosed SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 33, sequences corresponding to an upstream motif or *cis* element characteristic of PRL-FP111 as set forth in Figure 1 at residues 370-388, and 4491-4502, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding GR/PR as set forth in Figure 1 at residues 433-445, sequences corresponding to an upstream shear stress motif or *cis* element as set forth in Figure 1 at residues 446-451, 1288-1293, 3597-3602, 4771-4776, and 5240-5245, respectively, sequences corresponding to glucocorticoid response upstream motif or *cis* element as set forth in Figure 1 at residues 574-600, 1042-1056, 2444-2468, 2442-2269, 3536-3563, 4574-4593, 4595-



motif or *cis* element capable of binding SRY as set forth in Figure 1 at residues 4625-4634, a sequence corresponding to an upstream motif or *cis* element characteristic of GC2 as set forth in Figure 1 at residues 4678-4711, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA3 as set forth in Figure 1 at residues 4765-4769, a sequence corresponding to an upstream motif or *cis* element capable of MIR as set forth in Figure 1 at residues 4759-4954, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-HNF-1 as set forth in Figure 1 at residues 4923-4941, a sequence corresponding to a thyroid receptor upstream motif or *cis* element as set forth in Figure 1 at residues 5151-5156, and a sequence corresponding to an upstream motif or *cis* element capable of binding NF $\kappa$ B as set forth in Figure 1 at residues 5166-5175 may be used to define a pair of primers that can be used with the polymerase chain reaction (Mullis, K. *et al.*, *Cold Spring Harbor Symp. Quant. Biol.* 51:263-273 (1986); Erlich H. *et al.*, EP 50,424; EP 84,796, EP 258,017, EP 237,362; Mullis, K., EP 201,184; Mullis K. *et al.*, US 4,683,202; Erlich, H., US 4,582,788; and Saiki, R. *et al.*, US 4,683,194)) to amplify and obtain any desired TIGR gene DNA molecule or fragment.

The TIGR promoter sequence(s) and TIGR flanking sequences can also be obtained by incubating oligonucleotide probes of TIGR oligonucleotides with members of genomic human libraries and recovering clones that hybridize to the probes. In a second embodiment, methods of "chromosome walking," or 3' or 5' RACE may be used (Frohman, M.A. *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)* 85:8998-9002 (1988), herein incorporated by reference); Ohara, O. *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)* 86:5673-5677 (1989), herein incorporated by reference) to obtain such sequences.

## II. Uses of the Molecules of the Invention in the Diagnosis and Prognosis of Glaucoma and Related Diseases

A particularly desired use of the present invention relates to the diagnosis of glaucoma, POAG, pigmentary glaucoma, high tension glaucoma and low tension glaucoma and their related diseases. Another particularly desired use of the present invention relates to the prognosis of glaucoma, POAG, pigmentary glaucoma, high tension glaucoma and low tension glaucoma and their related diseases. As used herein the term "glaucoma" includes both primary glaucomas, secondary glaucomas, juvenile glaucomas, congenital glaucomas, and familial glaucomas, including, without limitation, pigmentary glaucoma, high tension glaucoma and low tension glaucoma and their related diseases. As indicated above, methods for diagnosing or prognosing glaucoma suffer from inaccuracy, or require multiple examinations. The molecules of the present invention may be used to define superior assays for glaucoma. Quite apart from such usage, the molecules of the present invention may be used to diagnosis or predict an individual's sensitivity to elevated intraocular pressure upon administration of steroids such as

glucocorticoids or corticosteroids, or anti-inflammatory steroids). Dexamethasone, cortisol and prednisolone are preferred steroids for this purpose. Medical conditions such as inflammatory and allergic disorders, as well as organ transplantation recipients, benefit from treatment with glucocorticoids. Certain individuals exhibit an increased IOP response to such steroids (i.e., "steroid sensitivity"), which is manifested by an undesired increase in intraocular pressure. The present invention may be employed to diagnosis or predict such sensitivity, as well as glaucoma and related diseases.

In a first embodiment, the TIGR molecules of the present invention are used to determine whether an individual has a mutation affecting the level (i.e., the concentration of TIGR mRNA or protein in a sample, etc.) or pattern (i.e., the kinetics of expression, rate of decomposition, stability profile, etc.) of the TIGR expression (collectively, the "TIGR response" of a cell or bodily fluid) (for example, a mutation in the TIGR gene, or in a regulatory region(s) or other gene(s) that control or affect the expression of TIGR), and being predictive of individuals who would be predisposed to glaucoma (prognosis), related diseases, or steroid sensitivity. As used herein, the TIGR response manifested by a cell or bodily fluid is said to be "altered" if it differs from the TIGR response of cells or of bodily fluids of normal individuals. Such alteration may be manifested by either abnormally increased or abnormally diminished TIGR response. To determine whether a TIGR response is altered, the TIGR response manifested by the cell or bodily fluid of the patient is compared with that of a similar cell sample (or bodily fluid sample) of normal individuals. As will be appreciated, it is not necessary to re-determine the TIGR response of the cell sample (or bodily fluid sample) of normal individuals each time such a comparison is made; rather, the TIGR response of a particular individual may be compared with previously obtained values of normal individuals.

In one sub-embodiment, such an analysis is conducted by determining the presence and/or identity of polymorphism(s) in the TIGR gene or its flanking regions which are associated with glaucoma, or a predisposition (prognosis) to glaucoma, related diseases, or steroid sensitivity. As used herein, the term "TIGR flanking regions" refers to those regions which are located either upstream or downstream of the TIGR coding region.

Any of a variety of molecules can be used to identify such polymorphism(s). In one embodiment, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 33, sequences corresponding to an upstream motif or *cis* element characteristic of PRL-FP111 as set forth in Figure 1 at residues 370-388, and 4491-4502, respectively, a sequence corresponding to an upstream motif or *cis*

element capable of binding GR/PR as set forth in Figure 1 at residues 433-445, sequences corresponding to an upstream shear stress motif or *cis* element as set forth in Figure 1 at residues 446-451, 1288-1293, 3597-3602, 4771-4776, and 5240-5245, respectively, sequences corresponding to glucocorticoid response upstream motif or *cis* element as set forth in Figure 1 at residues 574-600, 1042-1056, 2444-2468, 2442-2269, 3536-3563, 4574-4593, 4595-4614, 4851-4865, 4844-4864, 5079-5084, 5083-5111, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding CBE as set forth in Figure 1 at residues 735-746, a sequence corresponding to an upstream motif or *cis* element capable of binding NFE as set forth in Figure 1 at residues 774-795, a sequence corresponding to an upstream motif or *cis* element capable of binding KTF.1-CS as set forth in Figure 1 at residues 843-854, a sequence corresponding to an upstream motif or *cis* element capable of binding PRE is set forth in Figure 1 at residues 987-1026, a sequence corresponding to an upstream motif or *cis* element capable of binding ETF-EGFR as set forth in Figure 1 at residues 1373-1388, a sequence corresponding to an upstream motif or *cis* element capable of binding SRE-cFos as set forth in Figure 1 at residues 1447-1456, a sequence corresponding to an upstream motif or *cis* element capable of binding Alu as set forth in Figure 1 at residues 1331-1550, a sequence corresponding to an upstream motif or *cis* element capable of binding VBP as set forth in Figure 1 at residues 1786-1797, a sequence corresponding to an upstream motif or *cis* element capable of binding Malt-CS as set forth in Figure 1 at residues 1832-1841, sequences corresponding to an upstream motif or *cis* element capable of binding ERE as set forth in Figure 1 at residues 2167-2195, 3413-3429, and 3892-3896, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-mutagen as set forth in Figure 1 at residues 2329-2338, a sequence corresponding to an upstream motif or *cis* element capable of binding myc-PRF as set forth in Figure 1 at residues 2403-2416, sequences corresponding to an upstream motif or *cis* element capable of binding AP2 as set forth in Figure 1 at residues 2520-2535 and 5170-5187, respectively, sequences corresponding to an upstream motif or *cis* element capable of binding HSTF as set forth in Figure 1 at residues 2622-2635, and 5105-5132, respectively, a sequence corresponding to an upstream motif or *cis* element characteristic of SBF as set forth in Figure 1 at residues 2733-2743, sequences corresponding to an upstream motif or *cis* element capable of binding NF-1 as set forth in Figure 1 at residues 2923-2938, 4144-4157, and 4887-4900, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-MHCIIA/B as set forth in Figure 1 at residues 2936-2944, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA1 as set forth in Figure 1 at residues 3285-3298, a sequence corresponding to an upstream motif or *cis* element capable of binding ICS as set forth in Figure 1 at residues 3688-3699, a sequence corresponding to an upstream motif or *cis* element capable of binding ISGF2 as set forth in Figure 1 at residues 4170-4179, a sequence

corresponding to an upstream motif or *cis* element capable of binding zinc as set forth in Figure 1 at residues 4285-4293, a sequence corresponding to an upstream motif or *cis* element characteristic of CAP/CRP-galO as set forth in Figure 1 at residues 4379-4404, sequences corresponding to an upstream motif or *cis* element capable of binding AP1 as set forth in Figure 5 1 at residues 4428-4434, and 4627-4639, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding SRY as set forth in Figure 1 at residues 4625-4634, a sequence corresponding to an upstream motif or *cis* element characteristic of GC2 as set forth in Figure 1 at residues 4678-4711, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA3 as set forth in Figure 1 at residues 4765-4769, a sequence corresponding to an upstream motif or *cis* element capable of MIR as set forth in Figure 10 1 at residues 4759-4954, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-HNF-1 as set forth in Figure 1 at residues 4923-4941, a sequence corresponding to a thyroid receptor upstream motif or *cis* element as set forth in Figure 1 at residues 5151-5156, and a sequence corresponding to an upstream motif or *cis* element capable of binding NF $\kappa$ B as 15 set forth in Figure 1 at residues 5166-5175 (or a sub-sequence thereof) may be employed as a marker nucleic acid molecule to identify such polymorphism(s).

Alternatively, such polymorphisms can be detected through the use of a marker nucleic acid molecule or a marker protein that is genetically linked to (i.e., a polynucleotide that co-segregates with) such polymorphism(s). As stated above, the TIGR gene and/or a sequence or 20 sequences that specifically hybridize to the TIGR gene have been mapped to chromosome 1q, 21-32, and more preferably to the TIGR gene located at chromosome 1, q21-27, and more preferably to the TIGR gene located at chromosome 1, q22-26, and most preferably to the TIGR gene located at chromosome 1, q24. In a preferred aspect of this embodiment, such marker nucleic acid molecules will have the nucleotide sequence of a polynucleotide that is closely genetically 25 linked to such polymorphism(s) (e.g., markers located at chromosome 1, q19-25 (and more preferably chromosome 1, q23-25, and most preferably chromosome 1, q24).

Localization studies using a Stanford G3 radiation hybrid panel mapped the TIGR gene with the D1S2536 marker nucleic acid molecules at the D1S2536 locus with a LOD score of 6.0. Other marker nucleic acid molecules in this region include: D1S210; D1S1552; D1S2536; 30 D1S2790; SHGC-12820; and D1S2558. Other polynucleotide markers that map to such locations are known and can be employed to identify such polymorphism(s).

The genomes of animals and plants naturally undergo spontaneous mutation in the course of their continuing evolution (Gusella, J.F., *Ann. Rev. Biochem.* 55:831-854 (1986)). A "polymorphism" in the TIGR gene or its flanking regions is a variation or difference in the 35 sequence of the TIGR gene or its flanking regions that arises in some of the members of a

species. The variant sequence and the "original" sequence co-exist in the species' population. In some instances, such co-existence is in stable or quasi-stable equilibrium.

A polymorphism is thus said to be "allelic," in that, due to the existence of the polymorphism, some members of a species may have the original sequence (i.e. the original "allele") whereas other members may have the variant sequence (i.e. the variant "allele"). In the simplest case, only one variant sequence may exist, and the polymorphism is thus said to be di-allelic. In other cases, the species' population may contain multiple alleles, and the polymorphism is termed tri-allelic, etc. A single gene may have multiple different unrelated polymorphisms. For example, it may have a di-allelic polymorphism at one site, and a multi-allelic polymorphism at another site.

The variation that defines the polymorphism may range from a single nucleotide variation to the insertion or deletion of extended regions within a gene. In some cases, the DNA sequence variations are in regions of the genome that are characterized by short tandem repeats (STRs) that include tandem di- or tri-nucleotide repeated motifs of nucleotides. Polymorphisms characterized by such tandem repeats are referred to as "variable number tandem repeat" ("VNTR") polymorphisms. VNTRs have been used in identity and paternity analysis (Weber, J.L., U.S. Patent 5,075,217; Armour, J.A.L. et al., *FEBS Lett.* 307:113-115 (1992); Jones, L. et al., *Eur. J. Haematol.* 39:144-147 (1987); Horn, G.T. et al., PCT Application WO91/14003; Jeffreys, A.J., European Patent Application 370,719; Jeffreys, A.J., U.S. Patent 5,175,082); Jeffreys, A.J. et al., *Nature* 316:76-79 (1985); Gray, I.C. et al., *Proc. R. Acad. Soc. Lond.* 243:241-253 (1991); Moore, S.S. et al., *Genomics* 10:654-660 (1991); Jeffreys, A.J. et al., *Anim. Genet.* 18:1-15 (1987); Hillel, J. et al., *Anim. Genet.* 20:145-155 (1989); Hillel, J. et al., *Genet.* 124:783-789 (1990)).

In an alternative embodiment, such polymorphisms can be detected through the use of a marker nucleic acid molecule that is physically linked to such polymorphism(s). For this purpose, marker nucleic acid molecules comprising a nucleotide sequence of a polynucleotide located within 1 mb of the polymorphism(s), and more preferably within 100 kb of the polymorphism(s), and most preferably within 10 kb of the polymorphism(s) can be employed. Examples of such marker nucleic acids are set out in SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25.

In another embodiment a marker nucleic acid will be used that is capable of specifically detecting *TIGRmt1*, *TIGRmt2*, *TIGRmt3*, *TIGRmt4*, *TIGRmt5*, *TIGRmt11*, *TIGRsv1*, or a combination of these mutations. Methods to detect base(s) substitutions, base(s) deletions and

base(s) additions are known in the art (i.e. methods to genotype an individual). For example, "Genetic Bit Analysis ("GBA") method is disclosed by Goelet, P. *et al.*, WO 92/15712, herein incorporated by reference, may be used for detecting the single nucleotide polymorphisms of the present invention. GBA is a method of polymorphic site interrogation in which the nucleotide sequence information surrounding the site of variation in a target DNA sequence is used to design an oligonucleotide primer that is complementary to the region immediately adjacent to, but not including, the variable nucleotide in the target DNA. The target DNA template is selected from the biological sample and hybridized to the interrogating primer. This primer is extended by a single labeled dideoxynucleotide using DNA polymerase in the presence of two, and preferably all four chain terminating nucleoside triphosphate precursors. Cohen, D. *et al.*, (PCT Application WO91/02087) describes a related method of genotyping.

Other primer-guided nucleotide incorporation procedures for assaying polymorphic sites in DNA have been described (Kornher, J. S. *et al.*, *Nucl. Acids. Res.* 17:7779-7784 (1989), herein incorporated by reference; Sokolov, B. P., *Nucl. Acids Res.* 18:3671 (1990), herein incorporated by reference; Syvänen, A.-C., *et al.*, *Genomics* 8:684 - 692 (1990), herein incorporated by reference; Kuppuswamy, M.N. *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)* 88:1143-1147 (1991), herein incorporated by reference; Prezant, T.R. *et al.*, *Hum. Mutat.* 1:159-164 (1992), herein incorporated by reference; Uguzzoli, L. *et al.*, *GATA* 9:107-112 (1992), herein incorporated by reference; Nyrén, P. *et al.*, *Anal. Biochem.* 208:171-175 (1993), herein incorporated by reference).

The detection of polymorphic sites in a sample of DNA may be facilitated through the use of nucleic acid amplification methods. Such methods specifically increase the concentration of polynucleotides that span the polymorphic site, or include that site and sequences located either distal or proximal to it. Such amplified molecules can be readily detected by gel electrophoresis or other means.

Another preferred method of achieving such amplification employs the polymerase chain reaction ("PCR") (Mullis, K. *et al.*, *Cold Spring Harbor Symp. Quant. Biol.* 51:263-273 (1986); Erlich H. *et al.*, European Patent Appln. 50,424; European Patent Appln. 84,796, European Patent Application 258,017, European Patent Appln. 237,362; Mullis, K., European Patent Appln. 201,184; Mullis K. *et al.*, U.S. Patent No. 4,683,202; Erlich, H., U.S. Patent No. 4,582,788; and Saiki, R. *et al.*, U.S. Patent No. 4,683,194), using primer pairs that are capable of hybridizing to the proximal sequences that define a polymorphism in its double-stranded form.

In lieu of PCR, alternative methods, such as the "Ligase Chain Reaction" ("LCR") may be used (Barany, F., *Proc. Natl. Acad. Sci. (U.S.A.)* 88:189-193 (1991)). LCR uses two pairs of oligonucleotide probes to exponentially amplify a specific target. The sequences of each pair of oligonucleotides is selected to permit the pair to hybridize to abutting sequences of the same

strand of the target. Such hybridization forms a substrate for a template-dependent ligase. As with PCR, the resulting products thus serve as a template in subsequent cycles and an exponential amplification of the desired sequence is obtained.

LCR can be performed with oligonucleotides having the proximal and distal sequences of the same strand of a polymorphic site. In one embodiment, either oligonucleotide will be designed to include the actual polymorphic site of the polymorphism. In such an embodiment, the reaction conditions are selected such that the oligonucleotides can be ligated together only if the target molecule either contains or lacks the specific nucleotide that is complementary to the polymorphic site present on the oligonucleotide. Alternatively, the oligonucleotides may be selected such that they do not include the polymorphic site (see, Segev, D., PCT Application WO 90/01069).

The "Oligonucleotide Ligation Assay" ("OLA") may alternatively be employed (Landegren, U. *et al.*, *Science* 241:1077-1080 (1988)). The OLA protocol uses two oligonucleotides which are designed to be capable of hybridizing to abutting sequences of a single strand of a target. OLA, like LCR, is particularly suited for the detection of point mutations. Unlike LCR, however, OLA results in "linear" rather than exponential amplification of the target sequence.

Nickerson, D.A. *et al.*, have described a nucleic acid detection assay that combines attributes of PCR and OLA (Nickerson, D.A. *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)* 87:8923-8927 (1990). In this method, PCR is used to achieve the exponential amplification of target DNA, which is then detected using OLA. In addition to requiring multiple, and separate, processing steps, one problem associated with such combinations is that they inherit all of the problems associated with PCR and OLA.

Schemes based on ligation of two (or more) oligonucleotides in the presence of nucleic acid having the sequence of the resulting "di-oligonucleotide", thereby amplifying the di-oligonucleotide, are also known (Wu, D.Y. *et al.*, *Genomics* 4:560 (1989)), and may be readily adapted to the purposes of the present invention.

Other known nucleic acid amplification procedures, such as allele-specific oligomers, branched DNA technology, transcription-based amplification systems, or isothermal amplification methods may also be used to amplify and analyze such polymorphisms (Malek, L.T. *et al.*, U.S. Patent 5,130,238; Davey, C. *et al.*, European Patent Application 329,822; Schuster *et al.*, U.S. Patent 5,169,766; Miller, H.I. *et al.*, PCT appln. WO 89/06700; Kwoh, D. *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)* 86:1173 (1989); Gingras, T.R. *et al.*, PCT application WO 88/10315; Walker, G.T. *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)* 89:392-396 (1992)). All the foregoing nucleic acid amplification methods could be used to predict or diagnose glaucoma.

The identification of a polymorphism in the TIGR gene, or flanking sequences up to about 5,000 base from either end of the coding region, can be determined in a variety of ways. By correlating the presence or absence of glaucoma in an individual with the presence or absence of a polymorphism in the TIGR gene or its flanking regions, it is possible to diagnose the 5 predisposition (prognosis) of an asymptomatic patient to glaucoma, related diseases, or steroid sensitivity. If a polymorphism creates or destroys a restriction endonuclease cleavage site, or if it results in the loss or insertion of DNA (e.g., a VNTR polymorphism), it will alter the size or profile of the DNA fragments that are generated by digestion with that restriction endonuclease. As such, individuals that possess a variant sequence can be distinguished from those having the 10 original sequence by restriction fragment analysis. Polymorphisms that can be identified in this manner are termed "restriction fragment length polymorphisms" ("RFLPs"). RFLPs have been widely used in human and animal genetic analyses (Glassberg, J., UK patent Application 2135774; Skolnick, M.H. *et al.*, *Cytogen. Cell Genet.* 32:58-67 (1982); Botstein, D. *et al.*, *Ann. J. Hum. Genet.* 32:314-331 (1980); Fischer, S.G *et al.* (PCT Application WO90/13668); Uhlen, 15 M., PCT Application WO90/11369)). The role of TIGR in glaucoma pathogenesis indicates that the presence of genetic alterations (e.g., DNA polymorphisms) that affect the TIGR response can be employed to predict glaucoma .

A preferred method of achieving such identification employs the single-strand conformational polymorphism (SSCP) approach. The SSCP technique is a method capable of 20 identifying most sequence variations in a single strand of DNA, typically between 150 and 250 nucleotides in length (Elles, *Methods in Molecular Medicine: Molecular Diagnosis of Genetic Diseases*, Humana Press (1996), herein incorporated by reference); Orita *et al.*, *Genomics* 5: 874-879 (1989), herein incorporated by reference). Under denaturing conditions a single strand of DNA will adopt a conformation that is uniquely dependent on its sequence conformation. This 25 conformation usually will be different, even if only a single base is changed. Most conformations have been reported to alter the physical configuration or size sufficiently to be detectable by electrophoresis. A number of protocols have been described for SSCP including, but not limited to Lee *et al.*, *Anal. Biochem.* 205: 289-293 (1992), herein incorporated by reference; Suzuki *et al.*, *Anal. Biochem.* 192: 82-84 (1991), herein incorporated by reference; Lo 30 *et al.*, *Nucleic Acids Research* 20: 1005-1009 (1992), herein incorporated by reference; Sarkar *et al.*, *Genomics* 13: 441-443 (1992), herein incorporated by reference).

In accordance with this embodiment of the invention, a sample DNA is obtained from a patient. In a preferred embodiment, the DNA sample is obtained from the patient's blood. However, any source of DNA may be used. The DNA is subjected to restriction endonuclease 35 digestion. TIGR is used as a probe in accordance with the above-described RFLP methods. By comparing the RFLP pattern of the TIGR gene obtained from normal and glaucomatous patients,

one can determine a patient's predisposition (prognosis) to glaucoma. The polymorphism obtained in this approach can then be cloned to identify the mutation at the coding region which alters the protein's structure or regulatory region of the gene which affects its expression level. Changes involving promoter interactions with other regulatory proteins can be identified by, for 5 example, gel shift assays using HTM cell extracts, fluid from the anterior chamber of the eye, serum, etc. Interactions of TIGR protein in glaucomatous cell extracts, fluid from the anterior chamber of the eye, serum, etc. can be compared to control samples to thereby identify changes in those properties of TIGR that relate to the pathogenesis of glaucoma. Similarly such extracts and fluids as well as others (blood, etc.) can be used to diagnosis or predict steroid sensitivity.

10 Several different classes of polymorphisms may be identified through such methods. Examples of such classes include: (1) polymorphisms present in the TIGR cDNA of different individuals; (2) polymorphisms in non-translated TIGR gene sequences, including the promoter or other regulatory regions of the TIGR gene; (3) polymorphisms in genes whose products interact with TIGR regulatory sequences; (4) polymorphisms in gene sequences whose products 15 interact with the TIGR protein, or to which the TIGR protein binds.

In an alternate sub-embodiment, the evaluation is conducted using oligonucleotide "probes" whose sequence is complementary to that of a portion of SEQ ID NO: 1, SEQ ID NO: 2 SEQ ID NO: 3, SEQ ID NO: 4, or SEQ ID NO: 5. Such molecules are then incubated with cell extracts of a patient under conditions sufficient to permit nucleic acid hybridization.

20 In one sub-embodiment of this aspect of the present invention, one can diagnose or predict glaucoma, related diseases and steroid sensitivity by ascertaining the TIGR response in a biopsy (or a macrophage or other blood cell sample), or other cell sample, or more preferably, in a sample of bodily fluid (especially, blood, serum, plasma, tears, buccal cavity, etc.). Since the TIGR gene is induced in response to the presence of glucocorticoids, a highly preferred 25 embodiment of this method comprises ascertaining such TIGR response prior to, during and/or subsequent to, the administration of a glucocorticoid. Thus, by way of illustration, glaucoma could be diagnosed or predicted by determining whether the administration of a glucocorticoid (administered topically, intraocularly, intramuscularly, systemically, or otherwise) alters the TIGR response of a particular individual, relative to that of normal individuals. Most preferably, 30 for this purpose, at least a "TIGR gene-inducing amount" of the glucocorticoid will be provided. As used herein, a TIGR gene-inducing amount of a glucocorticoid is an amount of glucocorticoid sufficient to cause a detectable induction of TIGR expression in cells of glaucomatous or non-glaucomatous individuals.

Generating Cells, Vectors, and Expressed Proteins Using Agents of the Invention

The present invention also relates to methods for obtaining a recombinant host cell, especially a mammalian host cell, comprising introducing into a host cell exogenous genetic material comprising a nucleic acid of the invention. The present invention also relates to an insect cell comprising a recombinant vector having a nucleic acid of the invention. The present invention also relates to methods for obtaining a recombinant host cell, comprising introducing exogenous genetic material comprising a nucleic acid of the invention via homologous recombination. Through homologous recombination, the promoter and 5' flanking sequences of the TIGR gene described here can be used in gene activation methods to produce a desired gene product in host cells (*see, for example*, U.S. Patent 5,733,746, specifically incorporated herein by reference). The specific expression of the TIGR gene in TM cells afforded by the TIGR promoter region DNA can, thus, be transferred via homologous recombination to express other gene products in a similar fashion. Some of these other gene products may be therapeutic proteins that address diseases related to increased IOP or glaucoma. Methods for selecting and using the promoter and 5' flanking sequence for the gene targeting technique involved in the gene activation method are known in the art. Depending upon the nature of the modification and associated targeting construct, various techniques may be employed for identifying targeted integration. Conveniently, the DNA may be digested with one or more restriction enzymes and the fragments probed with an appropriate DNA fragment, which will identify the properly sized restriction fragment associated with integration.

The sequence to be integrated into the host may be introduced by any convenient means, which includes calcium precipitated DNA, spheroplast fusion, transformation, electroporation, biolistics, lipofection, microinjection, or other convenient means. Where an amplifiable gene is being employed, the amplifiable gene may serve as the selection marker for selecting hosts into which the amplifiable gene has been introduced. Alternatively, one may include with the amplifiable gene another marker, such as a drug resistance marker, e.g. neomycin resistance (G418 in mammalian cells), hygromycin resistance etc., or an auxotrophy marker (HIS3, TRP1, LEU2, URA3, ADE2, LYS2, etc.) for use in yeast cells.

For example, homologous recombination constructs can be prepared where the amplifiable gene will be flanked, normally on both sides, with DNA homologous with the DNA of the target region, here the TIGR sequences. Depending upon the nature of the integrating DNA and the purpose of the integration, the homologous DNA will generally be within 100 kb, usually 50 kb, preferably about 25 kb, of the transcribed region of the target gene, more preferably within 2 kb of the target gene. The homologous DNA may include the 5'-upstream region outside of the transcriptional regulatory region or enhancer sequences, transcriptional

initiation sequences, adjacent sequences, or the like. The homologous region may include a portion of the coding region, where the coding region may be comprised only of an open reading frame or of combination of exons and introns. The homologous region may also comprise all or a portion of an intron, where all or a portion of one or more exons may also be present.

- 5 Alternatively, the homologous region may comprise the 3'-region, so as to comprise all or a portion of the transcriptional termination region, or the region 3' of this region. The homologous regions may extend over all or a portion of the target gene or be outside the target gene comprising all or a portion of the transcriptional regulatory regions and/or the structural gene.

The integrating constructs may be prepared in accordance with conventional ways, where  
10 sequences may be synthesized, isolated from natural sources, manipulated, cloned, ligated, subjected to in vitro mutagenesis, primer repair, or the like. At various stages, the joined sequences may be cloned, and analyzed by restriction analysis, sequencing, or the like. Usually during the preparation of a construct where various fragments are joined, the fragments, intermediate constructs and constructs will be carried on a cloning vector comprising a  
15 replication system functional in a prokaryotic host, e.g., *E. coli*, and a marker for selection, e.g., biocide resistance, complementation to an auxotrophic host, etc. Other functional sequences may also be present, such as polylinkers, for ease of introduction and excision of the construct or portions thereof, or the like. A large number of cloning vectors are available such as pBR322, the pUC series, etc. These constructs may then be used for integration into the primary host.

20 DNA comprising a nucleic acid of the invention can be introduced into a host cell by a variety of techniques that include calcium phosphate/DNA co-precipitates, microinjection of DNA into the nucleus, electroporation, yeast protoplast fusion with intact cells, transfection, polycations, e.g., polybrene, polyornithine, etc., or the like. The DNA may be single or double stranded DNA, linear or circular. The various techniques for transforming cells are well known  
25 (see Keown *et al.*, *Methods Enzymol.* (1989), Keown *et al.*, *Methods Enzymol.* 185:527-537 (1990); Mansour *et al.*, *Nature* 336:348-352, (1988); all of which are herein incorporated by reference in their entirety).

In a preferred aspect, the invention relates to recombinant insect vectors and insect cells comprising a nucleic acid of the invention. In a particularly preferred aspect, a Baculovirus  
30 expression vector is used, introduced into an insect cell, and recombinant TIGR protein expressed. The recombinant TIGR protein may be the full length protein from human TM endothelial cells, a fusion protein comprising a substantial fragment of the full length protein, for example, at least about 20 contiguous amino acids to about 100 contiguous amino acids of the full length protein, or a variant TIGR protein or fusion protein produced by site-directed  
35 mutagenesis, DNA shuffling, or a similar technique. Generally, the variant TIGR proteins and the fusion proteins will retain at least one structural or functional characteristic of the full length

TIGR protein, such as the ability to bind the same antibody, the presence of the substantially similar leucine zipper region, or the ability to bind the same ligand or receptor on TM cells (*see* Nguyen *et al.*, *J. Biol. Chem.* 273:6341-6350 (1998), specifically incorporated herein by reference). Nucleic acids comprising the leucine zipper-encoding regions of the TIGR gene can 5 be identified by methods known in the art and can be used in combination with recombinant or synthetic methods to create ligand-receptor assays.

Examples of the preferred, recombinant insect vector, host cell, and TIGR protein of the invention were generated by ligating TIGR cDNA into the PVL1393 vector [Invitrogen]. This vector was transferred into Sf9 cells, the TIGR protein expressed and then purified (see U.S. 10 Patent 5,789,169 and Nguyen *et al.*, *J. Biol. Chem.* 273:6341-6350 (1998), both of which are specifically incorporated herein by reference in their entirety). An SDS-PAGE gel of the resulting proteins showed protein bands in the 55 kDa range, which were sequenced to confirm correct identity.

In preferred embodiments of the vectors, cells and related methods of the invention, a 15 TIGR fusion protein with GFP (green fluorescent protein) can be expressed in a TM cell line (*see* Nguyen, *et al.*, *J. Biol. Chem.* 273:6341-6350 (1998) and the references cited therein for primary TM cell culture and transfection methods). Transformed, cultured TM cells at log phase were 20 transfected with a TIGR-GFP fusion protein-encoding vector. The vector includes the CMV promoter to allow high expression, TIGR cDNA from the first ATG to the end of the protein-encoding region, a fluorescent protein tag (GFP) fused to the carboxy terminus of the TIGR-encoding sequence, and the G418 resistance gene. These elements, and their use, is known in the art or provided by this disclosure and its incorporated references. The construct is termed 25 TIGR1-GFP. The transfection was performed using calcium phosphate or Lipofectin techniques, as known in the art. Incubation at growth condition of 37°C, 8% CO<sub>2</sub>, for 6-18 hours followed. After the transfection, the DNA media was replaced by fresh growth media including G418, 30 which was changed twice weekly, until resistant colonies of cells outgrew the monolayer cells (about 10-15 days). The cell colonies were collected and propagated several passes to select for resistant, transformed cells. The expression of fluorescent TIGR-GFP fusion protein was tested for after several passes. One out of twenty selected colonies expressed high levels of the TIGR-GFP fusion protein.

In other preferred embodiments of the cells and methods of the invention, a transformed, immortalized TM cell line can be prepared using an SV40-derived vector. Primary cultured TM cells are transfected with an SV40 vector with a defect in the PsvOri, as known in the art. Briefly, primary cultured cells at log phase are transfected with PsvOri DNA using calcium 35 phosphate or Lipofectin and incubated at growth condition of 37°C, 8% CO<sub>2</sub> for 6-18 hours. The DNA media was replaced by fresh growth media and changed twice weekly until colonies of

immortalized cells outgrow the dying monolayer (about 10-15 days). The cell colonies are collected and propagated several passes to select for transformed cells.

### III. Methods of Administration

Some of the agents of the present invention can be formulated according to known methods to prepare pharmacologically acceptable compositions, whereby these materials, or their functional derivatives, having the desired degree of purity are combined in admixture with a physiologically acceptable carrier, excipient, or stabilizer. Such materials are non-toxic to recipients at the dosages and concentrations employed. The active component of such compositions may be agents, analogs or mimetics of such molecules. Where nucleic acid molecules are employed, such molecules may be sense, antisense or triplex oligonucleotides of the TIGR promoter, TIGR cDNA, TIGR intron, TIGR exon or TIGR gene.

A composition is said to be "pharmacologically acceptable" if its administration can be tolerated by a recipient patient. An agent is physiologically significant if its presence results in a detectable change in the physiology of a recipient patient.

Suitable vehicles and their formulation, inclusive of other human proteins, e.g., human serum albumin, are described, for example, in Remington's Pharmaceutical Sciences (16<sup>th</sup> ed., Osol, A., Ed., Mack, Easton PA (1980)).

If the composition is to be water soluble, it may be formulated in a buffer such as phosphate or other organic acid salt preferably at a pH of about 7 to 8. If the composition is only partially soluble in water, it may be prepared as a microemulsion by formulating it with a nonionic surfactant such as Tween, Pluronics, or PEG, e.g., Tween 80, in an amount of, for example, 0.04-0.05% (w/v), to increase its solubility. The term "water soluble" as applied to the polysaccharides and polyethylene glycols is meant to include colloidal solutions and dispersions. In general, the solubility of the cellulose derivatives is determined by the degree of substitution of ether groups, and the stabilizing derivatives useful herein should have a sufficient quantity of such ether groups per anhydroglucose unit in the cellulose chain to render the derivatives water soluble. A degree of ether substitution of at least 0.35 ether groups per anhydroglucose unit is generally sufficient. Additionally, the cellulose derivatives may be in the form of alkali metal salts, for example, the Li, Na, K or Cs salts.

Optionally other ingredients may be added such as antioxidants, e.g., ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinyl pyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine;

monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, or dextrans; chelating agents such as EDTA; and sugar alcohols such as mannitol or sorbitol.

Additional pharmaceutical methods may be employed to control the duration of action.

- 5 Controlled or sustained release preparations may be achieved through the use of polymers to complex or absorb the TIGR molecule(s) of the composition. The controlled delivery may be exercised by selecting appropriate macromolecules (for example polyesters, polyamino acids, polyvinyl pyrrolidone, ethylenevinylacetate, methylcellulose, carboxymethylcellulose, or protamine sulfate) and the concentration of macromolecules as well as the methods of incorporation in order to control release.

10 Sustained release formulations may also be prepared, and include the formation of microcapsular particles and implantable articles. For preparing sustained-release compositions, the TIGR molecule(s) of the composition is preferably incorporated into a biodegradable matrix or microcapsule. A suitable material for this purpose is a polylactide, although other polymers of 15 poly-(*a*-hydroxycarboxylic acids), such as poly-D-(-)-3-hydroxybutyric acid (EP 133,988A), can be used. Other biodegradable polymers include poly(lactones), poly(orthoesters), polyamino acids, hydrogels, or poly(orthocarbonates) poly(acetals). The polymeric material may also comprise polyesters, poly(lactic acid) or ethylene vinylacetate copolymers. For examples of sustained release compositions, see U.S. Patent No. 3,773,919, EP 58,481A, U.S. Patent No. 20 3,887,699, EP 158,277A, Canadian Patent No. 1176565, Sidman, U. *et al.*, *Biopolymers* 22:547 (1983), and Langer, R. *et al.*, *Chem. Tech.* 12:98 (1982).

25 Alternatively, instead of incorporating the TIGR molecule(s) of the composition into polymeric particles, it is possible to entrap these materials in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatine-microcapsules and poly(methylmethacrylate) microcapsules, respectively, or in colloidal drug delivery systems, for example, liposomes, albumin microspheres, microemulsions, nanoparticles, and nanocapsules or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences (1980).

30 In an alternative embodiment, liposome formulations and methods that permit intracellular uptake of the molecule will be employed. Suitable methods are known in the art, see, for example, Chicz, R.M. *et al.* (PCT Application WO 94/04557), Jaysena, S.D. *et al.* (PCT Application WO93/12234), Yarosh, D.B. (U.S. Patent No. 5,190,762), Callahan, M.V. *et al.* (U.S. Patent No. 5,270,052) and Gonzalezro, R.J. (PCT Application 91/05771), all herein incorporated by reference.

Having now generally described the invention, the same will be more readily understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting of the present invention, unless specified.

### EXAMPLE 1

5

#### Illustrative Single Strand Conformational Polymorphism Assay

Single strand conformational polymorphism (SSCP) screening is carried out according to the procedure of Hue *et al.*, *The Journal of Investigative Ophthalmology* 105.4: 529-632 (1995), herein incorporated by reference. SSCP primers are constructed corresponding to sequences found within the TIGR promoter and two of exons of TIGR. The following primers are constructed: forward primer "Sk-1a": 5'-TGA GGC TTC CTC TGG AAA C-3' (SEQ ID NO: 6); forward reverse primer "ca2": 5'-TGA AAT CAG CAC ACC AGT AG-3' (SEQ ID NO: 7); forward primer "CA2": 5'-GCA CCC ATA CCC CAA TAA TAG-3' (SEQ ID NO: 8); reverse primer "Pr+1": 5'-AGA GTT CCC CAG ATT TCA CC-3' (SEQ ID NO: 9); forward primer "Pr-1": 5'-ATC TGG GGA ACT CTT CTC AG-3' (SEQ ID NO: 10); reverse primer "Pr+2(4A2)": 5'-TAC AGT TGT TGC AGA TAC G-3' (SEQ ID NO: 11); forward primer "Pr-2(4A)": 5'-ACA ACG TAT CTG CAA CAA CTG-3' (SEQ ID NO: 12); reverse primer "Pr+3(4A)": 5'-TCA GGC TTA ACT GCA GAA CC-3' (SEQ ID NO: 13); forward primer "Pr-3(4A)": 5'-TTG GTT CTG GCA ATC C-3' (SEQ ID NO: 15); reverse primer "Pr+1(4A)": 5'-ACA GGG CTA TAT TGT GGG-3' (SEQ ID NO: 16); forward primer "KS1X": 5'-CCT GAG ATG CCA GCT GTC C-3' (SEQ ID NO: 17); reverse primer "SK1XX": 5'-CTG AAG CAT TAG AAG CCA AC-3' (SEQ ID NO: 18); forward primer "KS2a1": 5'-ACC TTG GAC CAG GCT GCC AG-3' (SEQ ID NO: 19); reverse primer "SK3" 5'-AGG TTT GTT CGA GTT CCA G-3' (SEQ ID NO: 20); forward primer "KS4": 5'-ACA ATT ACT GGC AAG TAT GG-3' (SEQ ID NO: 21); reverse primer "SK6A": 5'-CCT TCT CAG CCT TGC TAC C-3' (SEQ ID NO: 22); forward primer "KS5": 5'-ACA CCT CAG CAG ATG CTA CC-3' (SEQ ID NO: 23); reverse primer "SK8": 5'-ATG GAT GAC TGA CAT GGC C-3' (SEQ ID NO: 24); forward primer "KS6": 5'-AAG GAT GAA CAT GGT CAC C-3' (SEQ ID NO: 25).

30

The locations of primers: Sk-1a, ca2, CA2, Pr+1, Pr-1, Pr+2(4A2), Pr-2(4A), Pr+3(4A), Pr-3 (4A), Pr-3(4A), Pr+2(4A1), and Pr+1(4A) are diagrammatically set forth in Figure 4. The location of primers: KS1X, SK1XX, Ks2a1, SK3, KS4, SK6A, KS5, SK8, and KS6 are diagrammatically set forth in Figure 5.

35

Families with a history of POAG in Klamath Falls, Oregon, are screened by SSCP according to the method of Hue *et al.*, *The Journal of Investigative Ophthalmology* 105.4: 529-

632 (1995), herein incorporated by reference). SSCP primers SK-1a, ca2, CA2, Pr+1, Pr-2(4A), Pr+3(4A), SK1XX, and KS6 detect single strand conformational polymorphisms in this population. An SSCP is detected using SSCP primers Pr+3(4A) and Pr-2(4A). 70 family members of the Klamath Fall, Oregon are screened with these primers and the results are set forth in Table 1.

TABLE 1

	Total	SSCP+	SSCP-
Glaucoma positive individuals <sup>1</sup>	12	12	0
Glaucoma negative individuals	13	0	13
Spouses (glaucoma negative)	16	2	14
Others <sup>2</sup>	29	6	23

1 = glaucoma positive individuals as determined by IOP of greater than 25 mmHg

2 = unidentified glaucoma due to the age of the individual.

A second SSCP is detected using SSCP primers Pr+1 and CA2. 14 family members of the Klamath Fall, Oregon are screened with these primers. A characteristic polymorphism is found in the 6 affected family members but absent in the 8 unaffected members. A third SSCP is detected using SSCP primers ca2 and sk-1a. The same 14 family members of the Klamath Fall, Oregon that are screened with Pr+1 and CA2 are screened with ca2 and sk-1a primers. A characteristic polymorphism is found in the 6 affected family members but absent in the 8 unaffected members. A fourth SSCP is detected using SSCP primers KS6 and SK1XX. 22 family members of the Klamath Fall, Oregon and 10 members of a Portland, Oregon pedigree are screened with these primers. A polymorphism is found in exon 3. The results are as set forth in Table 2.

TABLE 2

	Total	SSCP+	SSCP-
<b>Klamath Fall, Oregon</b>			
Glaucoma positive individuals <sup>1</sup>	3	3	0
Glaucoma negative individuals	6	0	6
Others <sup>2</sup>	13	6	7
<b>Portland, Oregon</b>			
Glaucoma positive individuals <sup>1</sup>	6	6	0
Glaucoma negative individuals	4	0	4

Others <sup>2</sup>                    0        0        0

1 = glaucoma positive individuals as determined by IOP of greater than 25 mmHg

2 = unidentified glaucoma due to the age of the individual.

EXAMPLE 2TIGR Homologies

5 A novel "myosin-like" acidic protein termed myocilin is expressed predominantly in the photoreceptor cells of retina and is localized particularly in the rootlet and basal body of connecting cilium (Kubota *et al.*, Genomics 41: 360-369 (1997), herein incorporated by reference). The myocilin gene is mapped to human chromosome 1q23-q24. The coding region of myocilin is 100 percent homologous with TIGR.

10 Homology searches are performed by GCG (Genetics Computer Group, Madison, WI) and include the GenBank, EMBL, Swiss-Prot databases and EST analysis. Using the Blast search, the best fits are found with a stretch of 177 amino acids in the carboxy terminals for an extracellular mucus protein of the olfactory, olfactomedin and three olfactomedin-like species. The alignment presented in Figure 6 shows the TIGR homology (SEQ ID NO. 27) to an  
15 expressed sequence tag (EST) sequence from human brain (ym08h12.r1)(SEQ ID NO. 28)(The WashU-Merck EST Project, 1995); the Z domain of olfactomedin-related glycoprotein from rat brain (1B426bAMZ)(SEQ ID NO. 29)(Danielson *et al.*, *Journal of Neuroscience Research* 38: 468-478 (1994), herein incorporated by reference) and the olfactomedin from olfactory tissue of bullfrogs (ranofm) (SEQ ID NO. 30)(Yokoe and Anholt, *Proc. Natl. Acad. Sci.* 90: 4655-4659  
20 (1993), herein incorporated by reference; Snyder and Anholt, *Biochemistry* 30: 9143-9153 (1991), herein incorporated by reference). These domains share very similar amino acid positions as depicted in the consensus homology of Figure 6 (SEQ ID NO. 31), with the exception being the truncated human clone in which the position with respect to its full length sequence has not been established. No significant homology is found for the amino termini of  
25 these molecules.

EXAMPLE 3Identification of TIGRmt11

30 DNA samples were obtained from individuals noted for having elevated IOP in response to the administration of topical corticosteroids. Typically, the "Armaly" criteria is used to register IOP changes.

Genomic DNA from blood or buccal swabs were used for PCR amplification. The PCR reaction includes 95° C for 30 sec, for denaturation, 55° C for 30 sec, for annealing and 72° C for

30 sec for synthesis. The reaction was performed for 30 cycles with an additional cycle of 72° C for 5 min at the end.

The primer pair for the PCR reaction can include any pair that amplifies a specific region targeted for analyzing mutants or polymorphisms. Preferably, the amplified region will be from about 500 base pairs 5' of the start of transcription to the start of translation. More preferably, it will include an amplified region about 200 bp 5' of the start of transcription to about 10 base pairs 5' to the start of translation. Methods for determining amplification primer sequences from within a known sequence region are well known in the art. Exemplary methods include, but are not limited to, computer generated searches using programs such as Primer3 ([www-genome.wi.mit.edu/cgi-bin/primer/primer3.cgi](http://www-genome.wi.mit.edu/cgi-bin/primer/primer3.cgi)), STSPipeline ([www-genome.wi.mit.edu/cgi-bin/www-STS\\_Pipeline](http://www-genome.wi.mit.edu/cgi-bin/www-STS_Pipeline)), or GeneUp (Pesole, *et al.*, *BioTechniques* 25:112-123 (1998)).

In an especially preferred embodiment, this amplified region will be from position 5044 of SEQ ID NO: 3 to about 5327 of SEQ ID NO: 3, which will thus employ primers of the sequence of about 5044 to about 5066 and the sequence of about 5309 to about 5327 of SEQ ID NO: 3, or the complement. In one embodiment, the complement of the sequence from about 5309 to about 5327 is used as one of the primers and the sequence from about 5044 to about 5066 is used as the other primer.

For this example, the following primers were used: forward primer CA-2R (SEQ ID NO: 35 - 5' AACTATTATT GGGGTATGGG) and reverse primer Sk-la (SEQ ID NO: 36 - 5' TTGGTGAGGC TTCCTCTGC). The primers were labeled with a fluorescent dye IRD-800 by Li-Cor Technology and the PCR product (about 300 bp) was denatured by heat and subject to BESS assays to detect mutations.

BESS, or Base Excision Sequence Scanning, employed specific restriction enzyme that cleaves T position of single strand DNA. The cleavage will produce DNA fragments that could be observed by acrylamide gels. Based on this, a 'T mutation' will produce different cleavage pattern for the mutated strand compared to the normal strand. Since 95% of mutations involve a T mutation, this method is very practical. In addition to BESS, the amplified fragments can also be sequenced or compared by hybridization methods (microarray hybridization techniques or the sequencing-by-hybridization technique) in order to determine the exact nucleotide sequence, as known in the art.

Using this assay, patients exhibiting an increased IOP in response to topical corticosteroid treatments had an elevated level of a T mutation in one particular position, at about

160 bases 5' to the start of the TIGR coding region. The presence of this particular mutation, called TIGRmt11, therefore, indicated a specific genetic linkage to steroid sensitivity that manifests in at least a higher risk of increased IOP, and thus glaucoma, in response to steroid treatment.

5

**TABLE 3**

<u>Subject</u>	<u>Duration of CS Treatment</u>	<u>IOP (OD/OS)</u>	<u>Genotype (mt.11)</u>
1	1 year	38/30	+/-
2	3 weeks	25/28	++/+
3	2 weeks	28/28	++/+

CS= corticosteroid, topical treatment

(1 year) CS treatment 38/30 mm Hg, OD/OS; (3 weeks) CS treatment 25/28 mm Hg, OD/OS; (2 weeks) CS treatment 28/38 mm Hg, OD/OS

10

The sequence in SEQ ID NO: 33 ( CAAACAGACT TCCGGAAAGGT) identifies bases immediately adjacent to the single base polymorphism, which represents bases 5101 to 5120 of SEQ ID NO: 1, except that the underlined C in the TIGRmt11 sequence variant is substituted for the 'wild type' T, found in SEQ ID NO: 1.

#### EXAMPLE 4

##### Verification of Linkage Between TIGRmt11 and Risk of Glaucoma

15

Subjects are given standard topical dexamethasone eye drops (0.1%) four times a day, for four weeks. Pre-treatment and post-treatment IOP readings are taken and patients are classified as having high (>16mmHg), intermediate (6-16mmHg) or low (<6mmHg) IOP responses under the "Armaly" criteria. DNA samples are obtained from four subjects having high or intermediate IOP changes. Samples from several non-responder patients were also taken. The DNA samples were analyzed for the presence of the TIGRmt11 variant sequence, as discussed above. The results are given in Table 4.

20

TABLE 4

5

<u>Subject</u>	<u>Age</u>	<u>Classification</u>	<u>CS-IOP Response</u>	<u>Genotype (mt.11)</u>
1	47	OHT	Intermediate	+/-
2	28	POAG	High	+/-
3	46	POAG/OHT	High	+/-
4	15	Stevens-Johnson	High	+/-
5	Nr	Normal	Low	-/-
6	Nr	Normal	Low	-/-
7	Nr	Normal	Low	-/-

OHT = Ocular Hypertensive (began with a mild IOP elevation, no POAG)

POAG = Original diagnosis is primary open-angle glaucoma

POAG/OHT = Converted to POAG, from original diagnosis OHT

10

The data obtained indicates the association of TIGRmt.11 and the response to topical CS. Clearly, all the subjects with clinically identifiable responses to the CS treatment possessed the TIGRmt11 variant sequence while none of the subjects with the 'wild type' sequence, or a sequence that did not possess the TIGRmt11 variant, did not.

15

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features herein before set forth and as follows in the scope of the appended claims.

20

EXAMPLE 5TIGR 5' Region /Promoter Activity Assays and Methods for Detecting Cell Components Binding to TIGR Gene Sequences

5      The 283 base 5' fragment of the TIGR 5' region (SEQ ID NO: 37) is amplified from genomic DNA of a normal human subject as discussed in Example 3. The DNA is cloned into a pSEAP vector (Clontech, CA) so that transcription was under the control of the TIGR sequences.

10     More specifically, pSEAP2-enhancer vector is digested with SrfI to produce a blunt end. The 283 bp fragment is blunt end ligated to the vector using T4 ligase for 2 hours. The vector is transfected into DH5 cells to establish a plasmid clone, TMRE-1/pSEAP. PCR sequencing is used to verify the clone sequence as correct. Similarly, the equivalent genomic fragment amplified from a steroid responder sample, identified as mutant TIGR.mt11, is cloned in pSEAP2-enhancer and called clone TIGR.mt11/pSEAP.

15     HTM cells, Cos cells (COS-7), and HeLa cells (HeLa 229) are seeded at  $10^6$  cells per well and incubated with 1 ug of the plasmid DNA to transfect using Lipofectin reagent (GIBCO, LifeTechnologies, MD). Some samples of cells were also treated with dexamethasone (DEX). Then, 24, 48, and 72 hours after transfection, AP activity was measured. Cells are collected 20 using a buffer containing L-homoarginine and the chemiluminescent substrate CSPD and a chemiluminescent enhancer added to the samples. The expression levels are then recorded using a luminometer or by brief exposure to X-ray film. The results show that AP activity is present in HTM transfected cells within 24 hours and that the levels increase over 50 fold 48 and 72 hours after transfection. In contrast, HeLa and Cos cells show insignificant AP activity at the same 25 time points.

20     To detect cell components that specifically bind to TIGR sequences, the amplified genomic fragments are suitably labeled, such as by end-labeling with  $^{32}\text{P}$ dATP using T4 Kinase. Labeled fragments are then incubated with nuclear extracts of TM cells, +/- treatment with DEX (500nM) for 10 days, and HeLa cell extract (Stratagene, CA) for 15 minutes at 0°C. The samples 30 are then run on a low ionic strength, non-denaturing polyacrylamide gel. The gel is then dried and exposed to X-ray film overnight. The shift in mobility, apparent in Figure 9, demonstrates

the presence of DNA binding components from HTM cells, and that treatment with DEX changes the amount or strength of binding.

5

WHAT IS CLAIMED IS:

1. A method for diagnosing glaucoma in a patient which comprises the steps:
  - (A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, said first marker nucleic acid molecule comprising a nucleotide sequence of a polynucleotide that specifically hybridizes to a polynucleotide that is linked to a TIGR promoter, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient, wherein nucleic acid hybridization between said marker nucleic acid molecule, and said complementary nucleic acid molecule obtained from said patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting TIGR response in said patient;
  - (B) permitting hybridization between said marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient; and
  - (C) detecting the presence of said polymorphism, wherein the detection of said polymorphism is diagnostic of glaucoma.
2. A method for diagnosing glaucoma in a patient according to claim 1, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt1*.
3. A method for diagnosing glaucoma in a patient according to claim 1, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt2*.
4. A method for diagnosing glaucoma in a patient according to claim 1, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt3*.
5. A method for diagnosing glaucoma in a patient according to claim 1, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt4*.
6. A method for diagnosing glaucoma in a patient according to claim 1, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt5*.
7. A method for diagnosing glaucoma in a patient according to claim 1, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRsv1*.
8. A method for diagnosing glaucoma in a patient according to claim 1, further comprising a second marker nucleic acid molecule.
9. A method for diagnosing glaucoma in a patient according to claim 8, wherein said first marker nucleic acid molecule and said second marker nucleic acid molecule are selected from the group consisting of a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 10, a

nucleic acid molecule that comprises the sequence of SEQ ID NO: 11, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 14, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 15, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 16, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 17, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 19, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 20, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 21, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 23, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 24 and a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25.

10. A method for diagnosing glaucoma in a patient according to claim 9, wherein said first marker nucleic acid molecule and said second marker nucleic acid molecule are selected from the group consisting of a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18, and a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25

11. A method for diagnosing glaucoma in a patient according to claim 10, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12.

12. A method for diagnosing glaucoma in a patient according to claim 10, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8.

13. A method for diagnosing glaucoma in a patient according to claim 10, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6.

14. A method for diagnosing glaucoma in a patient according to claim 10, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID

NO: 18 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25.

15. A method for diagnosing steroid sensitivity in a patient which comprises the steps:

(A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, said marker nucleic acid molecule comprising a nucleotide sequence of a polynucleotide that is linked to a TIGR promoter, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient, wherein nucleic acid hybridization between said marker nucleic acid molecule, and said complementary nucleic acid molecule obtained from said patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting TIGR response in said patient;

(B) permitting hybridization between said TIGR-encoding marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient; and

(C) detecting the presence of said polymorphism, wherein the detection of said polymorphism is diagnostic of steroid sensitivity.

16. A method for diagnosing steroid sensitivity in a patient according to claim 15, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt1*.

17. A method for diagnosing steroid sensitivity in a patient according to claim 15, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt2*.

18. A method for diagnosing steroid sensitivity in a patient according to claim 15, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt3*.

19. A method for diagnosing steroid sensitivity in a patient according to claim 15, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt4*.

20. A method for diagnosing steroid sensitivity in a patient according to claim 15, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt5*.

21. A method for diagnosing steroid sensitivity in a patient according to claim 15, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRsv1*.

22. A method for diagnosing steroid sensitivity in a patient according to claim 15, further comprising a second marker nucleic acid molecule.

23. A method for diagnosing steroid sensitivity in a patient according to claim 22, wherein said first marker nucleic acid molecule and said second marker nucleic acid molecule are selected from the group consisting of a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 10, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 11, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12, a nucleic acid molecule that comprises

the sequence of SEQ ID NO: 13, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 14, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 15, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 16, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 17, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 19, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 20, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 21, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 22, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 23, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 24 and a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25.

24. A method for diagnosing steroid sensitivity in a patient according to claim 23, wherein said first marker nucleic acid molecule and said second marker nucleic acid molecule are selected from the group consisting of a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18, and a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25.

25. A method for diagnosing steroid sensitivity in a patient according to claim 24, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12.

26. A method for diagnosing glaucoma in a patient according to claim 24, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 5.

27. A method for diagnosing steroid sensitivity in a patient according to claim 24, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6.

28. A method for diagnosing steroid sensitivity in a patient according to claim 24, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25.

29. The method of claims 10 or 24, wherein said complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient has been amplified using a nucleic acid amplification method.
30. The method of claim 1, wherein said marker nucleic acid molecule is selected from the group consisting of D1S2536 marker nucleic acid, D1S210 marker nucleic acid, D1S1552 marker nucleic acid, D1S2536 marker nucleic acid D1S2790 marker nucleic acid, SHGC-12820 marker nucleic acid, and D1S2558 marker nucleic acid.
31. The method of claim 30, wherein said marker nucleic acid molecule is D1S2536 marker nucleic acid.
32. The method of claim 15, wherein said marker nucleic acid molecule is selected from the group consisting of D1S2536 marker nucleic acid, D1S210 marker nucleic acid, D1S1552 marker nucleic acid, D1S2536 marker nucleic acid D1S2790 marker nucleic acid, SHGC-12820 marker nucleic acid, and D1S2558 marker nucleic acid.
33. The method of claim 32, wherein said marker nucleic acid molecule is D1S2536 marker nucleic acid.
34. A nucleic acid molecule that comprises the sequence of SEQ ID NO: 1.
35. A recombinant DNA molecule containing a polynucleotide that specifically hybridizes to SEQ ID NO: 1.
36. A substantially purified molecule that specifically binds to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 1.
37. A nucleic acid molecule that comprises the sequence of SEQ ID NO: 3.
38. A recombinant DNA molecule containing a polynucleotide that specifically hybridizes to SEQ ID NO: 3.
39. A substantially purified molecule that specifically binds to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 3.
40. A nucleic acid molecule that comprises the sequence of SEQ ID NO: 4.
41. A recombinant DNA molecule containing a polynucleotide that specifically hybridizes to SEQ ID NO: 4.
42. A substantially purified molecule that specifically binds to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 4.
43. A nucleic acid molecule that comprises the sequence of SEQ ID NO: 5.
44. A recombinant DNA molecule containing a polynucleotide that specifically hybridizes to SEQ ID NO: 5.
45. A substantially purified molecule that specifically binds to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 5.
46. A nucleic acid molecule that comprises the sequence of SEQ ID NO: 26.

47. A recombinant DNA molecule containing a polynucleotide that specifically hybridizes to SEQ ID NO: 26.
48. A substantially purified molecule that specifically binds to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 26.
49. A substantially purified molecule that specifically binds to a nucleic acid molecule selected from the group consisting of a nucleic acid molecule that comprises a *cis* element characteristic of PRL-FP111, a nucleic acid molecule that comprises a glucocorticoid response *cis* element, a nucleic acid molecule that comprises a *cis* element characteristic of GR/PR, a nucleic acid molecule that comprises a shear stress response *cis* element, a nucleic acid molecule that comprises a glucocorticoid response *cis* element, a nucleic acid molecule that comprises a *cis* element characteristic of CBE, a nucleic acid molecule that comprises a *cis* element capable of binding NFE, a nucleic acid molecule that comprises a *cis* element capable of binding KTF.1-CS, a nucleic acid molecule that comprises a *cis* element characteristic of PRE, a nucleic acid molecule that comprises a *cis* element characteristic of ETF-EGFR, a nucleic acid molecule that comprises a *cis* element capable of binding SRE-cFos, a nucleic acid molecule that comprises a *cis* element capable of binding Alu, a nucleic acid molecule that comprises a *cis* element capable of binding VBP, a nucleic acid molecule that comprises a *cis* element characteristic of Malt-CS, a nucleic acid molecule that comprises a *cis* element capable of binding ERE, a nucleic acid molecule that comprises a *cis* element characteristic of NF-mutagen, a nucleic acid molecule that comprises a *cis* element capable of binding myc-PRF, a nucleic acid molecule that comprises a *cis* element capable of binding AP2, a nucleic acid molecule that comprises a *cis* element capable of binding HSTF, a nucleic acid molecule that comprises a *cis* element characteristic of SBF, a nucleic acid molecule that comprises a *cis* element capable of binding NF-1, a nucleic acid molecule that comprises a *cis* element capable of binding PEA1, a nucleic acid molecule that comprises a *cis* element characteristic of ICS, a nucleic acid molecule that comprises a *cis* element capable of binding ISGF2, a nucleic acid molecule that comprises a *cis* element capable of binding zinc, a nucleic acid molecule that comprises a *cis* element characteristic of CAP/CRP-galO, a nucleic acid molecule that comprises a *cis* element capable of binding AP1, a nucleic acid molecule that comprises a *cis* element capable of binding SRY, a nucleic acid molecule that comprises a *cis* element characteristic of GC2, a nucleic acid molecule that comprises a *cis* element capable of binding PEA3, a nucleic acid molecule that comprises a *cis* element characteristic of MIR, a nucleic acid molecule that comprises a *cis* element capable of binding NF-HNF-1, a nucleic acid molecule that comprises a thyroid receptor *cis* element, and a nucleic acid molecule that comprises a *cis* element capable of binding NF $\kappa$ B.

50. A method of treating glaucoma which comprises administering to a glaucomatous patient an effective amount of an agent capable of binding a *cis* element located within SEQ ID NO: 1.
51. The method of claim 50, wherein said agent inhibits the expression of a TIGR mRNA.
52. The method of claim 50, wherein said agent binds a DNA sequence within SEQ ID NO: 1.
53. The method of claim 50, wherein said agent binds a nucleic acid molecule that comprises a *cis* element characteristic of PRL-FP111, a nucleic acid molecule that comprises a glucocorticoid response *cis* element, a nucleic acid molecule that comprises a *cis* element characteristic of GR/PR, a nucleic acid molecule that comprises a shear stress response *cis* element, a nucleic acid molecule that comprises a glucocorticoid response *cis* element, a nucleic acid molecule that comprises a *cis* element characteristic of CBE, a nucleic acid molecule that comprises a *cis* element capable of binding NFE, a nucleic acid molecule that comprises a *cis* element capable of binding KTF-1-CS, a nucleic acid molecule that comprises a *cis* element characteristic of PRE, a nucleic acid molecule that comprises a *cis* element characteristic of ETF-EGFR, a nucleic acid molecule that comprises a *cis* element capable of binding SRE-cFos, a nucleic acid molecule that comprises a *cis* element characteristic of Alu, a nucleic acid molecule that comprises a *cis* element capable of binding VBP, a nucleic acid molecule that comprises a *cis* element characteristic of Malt-CS, a nucleic acid molecule that comprises a *cis* element capable of binding ERE, a nucleic acid molecule that comprises a *cis* element characteristic of NF-mutagen, a nucleic acid molecule that comprises a *cis* element capable of binding myc-PRF, a nucleic acid molecule that comprises a *cis* element capable of binding AP2, a nucleic acid molecule that comprises a *cis* element capable of binding HSTF, a nucleic acid molecule that comprises a *cis* element characteristic of SBF, a nucleic acid molecule that comprises a *cis* element capable of binding NF-1, a nucleic acid molecule that comprises a *cis* element capable of binding NF-MHCIIA/B, a nucleic acid molecule that comprises a *cis* element capable of binding PEA1, a nucleic acid molecule that comprises a *cis* element characteristic of ICS, a nucleic acid molecule that comprises a *cis* element capable of binding zinc, a nucleic acid molecule that comprises a *cis* element characteristic of CAP/CRP-galO, a nucleic acid molecule that comprises a *cis* element capable of binding AP1, a nucleic acid molecule that comprises a *cis* element capable of binding SRY, a nucleic acid molecule that comprises a *cis* element characteristic of GC2, a nucleic acid molecule that comprises a *cis* element capable of binding PEA3, a nucleic acid molecule that comprises a *cis* element characteristic of MIR, a nucleic acid molecule that comprises a *cis* element capable of binding NF-HNF-1, a nucleic acid molecule that comprises a thyroid receptor *cis* element, and a nucleic acid molecule that comprises a *cis* element capable of binding NFκB.

54. A method for prognosing glaucoma in a patient which comprises the steps:

(A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, said first marker nucleic acid molecule comprising a nucleotide sequence of a polynucleotide that specifically hybridizes to a polynucleotide that is linked to a TIGR promoter, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient, wherein nucleic acid hybridization between said marker nucleic acid molecule, and said complementary nucleic acid molecule obtained from said patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting TIGR response in said patient;

(B) permitting hybridization between said marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient; and

(C) detecting the presence of said polymorphism, wherein the detection of said polymorphism is prognostic of glaucoma.

55. A method for prognosing glaucoma in a patient according to claim 54, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt1*.

56. A method for prognosing glaucoma in a patient according to claim 54, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt2*.

57. A method for prognosing glaucoma in a patient according to claim 54, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt3*.

58. A method for prognosing glaucoma in a patient according to claim 54, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt4*.

59. A method for prognosing glaucoma in a patient according to claim 54, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt5*.

60. A method for prognosing glaucoma in a patient according to claim 54, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRsv1*.

61. A method for prognosing glaucoma in a patient according to claim 54, further comprising a second marker nucleic acid molecule.

62. A method for prognosing glaucoma in a patient according to claim 61, wherein said first marker nucleic acid molecule and said second marker nucleic acid molecule are selected from the group consisting of a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 10, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 11, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13, a nucleic acid molecule that comprises the sequence of SEQ ID

NO: 14, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 15, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 16, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 17, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 19, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 20, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 21, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 22, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 23, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 24 and a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25.

63. A method for diagnosing glaucoma in a patient according to claim 62, wherein said first marker nucleic acid molecule and said second marker nucleic acid molecule are selected from the group consisting of a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18, and a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25

64. A method for diagnosing glaucoma in a patient according to claim 63, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12.

65. A method for diagnosing glaucoma in a patient according to claim 63, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8.

66. A method for diagnosing glaucoma in a patient according to claim 63, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6.

67. A method for diagnosing glaucoma in a patient according to claim 63, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25.

68. The method of claim 54, wherein said marker nucleic acid molecule is selected from the group consisting of D1S2536 marker nucleic acid, D1S210 marker nucleic acid, D1S1552

marker nucleic acid, D1S2536 marker nucleic acid D1S2790 marker nucleic acid, SHGC-12820 marker nucleic acid, and D1S2558 marker nucleic acid.

69. The method of claim 68, wherein said marker nucleic acid molecule is D1S2536 marker nucleic acid.

70. A nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 33 and its complement, a region of SEQ ID NO: 33 or its complement that specifically hybridizes to a nucleic acid possessing the characteristic C to T substitution of the mt11 sequence variant, and a region of SEQ ID NO: 33 or its complement that specifically hybridizes to a nucleic acid possessing the characteristic C to T substitution of the TIGRmt11 sequence variant but does not specifically hybridize to a nucleic acid that does not possess the TIGRmt11 sequence variant under high stringency conditions.

71. A nucleic acid that specifically hybridizes to the nucleic acid of claim 70.

72. A vector comprising the nucleic acid of claim 70.

73. A cell comprising the nucleic acid of claim 70.

74. A method for detecting the presence or absence of the characteristic TIGRmt11 sequence variation in a sample containing DNA, comprising contacting a labeled nucleic acid of claim 70 with the DNA of the sample under hybridization conditions and determining the presence of hybrid nucleic acid molecules comprising the labeled nucleic acid.

75. A method for determining the presence of increased susceptibility to a glaucoma, to a progressive ocular hypertensive disorder resulting in loss of visual field, or the presence of steroid sensitivity in a patient, comprising the method of claim 74, wherein the sample containing DNA is derived from the patient.

76. The method of claim 75, which is performed during or after the patient is treated with a steroid compound.

77. The method of claim 75, which is performed prior to an administration of a steroid compound.

78. A kit for determining the presence of increased susceptibility to a glaucoma, to a progressive ocular hypertensive disorder resulting in loss of visual field, or the presence of

steroid sensitivity in a patient, comprising a labeled nucleic acid of claim 70 and a means for detecting hybridization with the labeled nucleic acid.

79. A nucleic acid comprising a nucleotide sequence selected from the group consisting of one of SEQ ID NO: 1-3 or 34, and a fragment of SEQ ID NO: 1-3, or 34 that possesses a functional regulatory region.

80. A cell comprising an introduced nucleic acid of the sequence as claimed in claim 79.

81. A vector comprising a nucleic acid as claimed in claim 79.

82. A method for detecting the specific binding of a molecule to a nucleic acid comprising providing a nucleic acid of claim 79, contacting the nucleic acid with a sample containing the molecule to be tested, and identifying binding of the molecule to the nucleic acid.

83. A method as claimed in claim 82, wherein the identifying step comprises a gel shift assay.

84. A method as claimed in claim 82, wherein the nucleic acid is labeled.

85. A method for detecting the presence of the TIGRmt11 sequence variation in a sample containing DNA, comprising providing amplification reaction primers that direct amplification of a selected nucleic acid region containing the T to C substitution of the TIGRmt11 sequence variant, amplifying the nucleic acid defined by the amplification reaction primers, and determining the presence or absence of the T to C substitution in the amplified nucleic acid.

86. The method of claim 85, wherein the determining the presence or absence of the T to C substitution comprises sequencing the amplified nucleic acid.

87. The method of claim 86, wherein the determining the presence or absence of the T to C substitution comprises a hybridization assay.

88. A method for determining the presence of increased susceptibility to a glaucoma, to a progressive ocular hypertensive disorder resulting in loss of visual field, or the presence of steroid sensitivity in a patient comprising the method of claim 85, wherein the sample containing DNA is derived from the patient.

89. A kit for determining the presence of increased susceptibility to a glaucoma, to a progressive ocular hypertensive disorder resulting in loss of visual field, or the presence of steroid sensitivity in a patient, comprising amplification reaction primers that direct amplification of a selected nucleic acid region containing the T to C substitution of the TIGRmt11 sequence variant and an enzyme for amplifying the region containing the T to C substitution.

90. A method for detecting a polymorphism in the 5' flanking region of a TIGR gene, comprising selecting amplification reaction primers from the group consisting of nucleic acids comprising nucleotide sequences SEQ ID NO: 6-25 or 35, or complements thereof, nucleotide sequences from a fragment of SEQ ID NO: 6-25 or 35, or their complements, and nucleotide sequences from an about 18 to an about 60 nucleotide fragment of the 5' flanking sequences in

SEQ ID NO: 1-3, or 34, or complements thereof, amplifying a selected nucleic acid region of the 5' flanking region defined by the amplification reaction primers in a sample of DNA, and comparing at least part of the sequence of the amplified nucleic acid with the sequence set forth in SEQ ID NO: 1-3.

91. A substantially purified nucleic acid molecule comprising SEQ ID NO: 37 or SEQ ID NO: 38.
92. The nucleic acid molecule of claim 91 that is capable of conferring tissue specific promoter activity.
93. A recombinant nucleic acid molecule comprising the nucleic acid molecule of claim 91.
94. A vector comprising a nucleic acid molecule of claim 91.
95. A cell comprising an introduced nucleic acid molecule, the introduced nucleic acid molecule comprising the nucleic acid molecule of claim 91.
96. A substantially purified nucleic acid molecule comprising a sequence having about 95% identity to SEQ ID NO: 37 or SEQ ID NO: 38.
97. The nucleic acid molecule of claim 96 that is capable of conferring a tissue specific promoter activity.
98. A recombinant nucleic acid molecule comprising the nucleic acid molecule of claim 96.
99. A vector comprising a nucleic acid molecule of claim 96.
100. A cell comprising an introduced nucleic acid molecule, the introduced nucleic acid molecule comprising the nucleic acid molecule of claim 96.
101. A substantially purified nucleic acid molecule comprising SEQ ID NO: 37 or SEQ ID NO: 38, or a variant thereof, capable of conferring tissue specific expression.
102. A recombinant nucleic acid molecule comprising the nucleic acid molecule of claim 101.
103. A vector comprising a nucleic acid molecule of claim 101.
104. A cell comprising an introduced nucleic acid molecule, the introduced nucleic acid molecule comprising the nucleic acid molecule of claim 101.
105. A method for identifying a protein or first compound that binds to a sequence of a TIGR gene, comprising incubating a nucleic acid molecule comprising SEQ ID NO: 37 or 38, or variant or either, or a region of SEQ ID NO: 3 or 34, with a composition containing the protein or first compound, and detecting the presence of binding to the nucleic acid molecule.

106. A method for identifying a second compound that modulates the binding of a protein or first compound to a TIGR gene sequence, comprising the steps of claim 105, further comprising adding the second compound to the nucleic acid molecule and comparing the binding detected with a control.

107. A method for identifying a protein or compound that modulates expression of a TIGR gene, comprising incubating a nucleic acid molecule comprising SEQ ID NO: 37 or 38, or variant of either, or a region of SEQ ID NO: 3 or 34, with a composition containing the protein or compound, and detecting the presence of binding to the nucleic acid molecule compared to a control.

108. The method of claim 107 wherein the nucleic acid molecule is contained within a cell.

109. A method for identifying a cellular component that modulates expression of a TIGR gene, comprising incubating a nucleic acid molecule comprising SEQ ID NO: 37 or 38, or variant of either, or a region of SEQ ID NO: 3 or 34, with an extract of a cell, and detecting the presence of specific binding to the nucleic acid molecule.

110. A method for identifying a compound that modulates steroid induction of a TIGR gene, comprising incubating a cell containing an introduced nucleic acid molecule comprising a TIGR 5' regulatory region with the compound, and detecting the expression of a gene linked to the TIGR 5' regulatory region.

111. The method of claim 110, wherein the 5' regulatory sequence comprises SEQ ID NO: 37 or 38, or variant of either, or a region of SEQ ID NO: 3 or 34.

1 ATC TTTGTTCA GTTACCTCAGG GCTATTATGA 33  
 34 AATGAAATGA GATAACCAAT GTGAAAAGTCC TATAAACTGT ATAGCCTCCA TTGGATGTA 93  
 94 TGTCTTTGGC AGGATGATAA AGAACAGGA AGAAGGAGTA TCCACGTTAG CCAAGTGTCC 153  
 154 AGGCTGTGTC TGCTCTTATT TTGAGTGACAG ATGTTGCTCC TGACAGAAGC TATTCTTCAG 213  
 214 GAAACATCAC ATCCAATATG GTAAATCCAT CAAACAGGAG CTAAGAAACA GGAATGAGAT 273  
 274 GGGCACTTGC CCAAGGAAAA ATGCCAGGAG AGCAAATAAT GATGAAAAT AAACCTTTCC 333  
 334 CTTTGTCCCC AATTCAGGA AAAATGATG AGGACCAAAA TCAATGAATA AGGAAAACAG 393  
     (Pr1.FPIII) CCTG AAAATGAATA AGAAA  
 394 CTCAGAAAAA AGATGTTTCC AAATTGGTAA TTAAGTATTG GTTCCCTGGG AAGAGACCTC 453  
     (PR/GR-MMTV) T GTTCTTTGG AA  
     (SSRE) GAGACC  
 454 CATGTGAGCT TGATGGAAA ATGGGAAAAA CGTCAAAAGC ATGATCTGAT CAGATCCAA 513  
 514 AGTGGATTAT TATTTAAAA ACCAGATGGC ATCACTCTGG GGAGGCAAGT TCAGGAAGGT 573  
 574 CATGTTAGCA AAGGACATAA CAATAACAGC AAAATCAAAA TTCCGCAAAT GCAGGAGGAA 633  
     CCTTTAG-A AAGGACAAAA CAGAATG (nGRE-PRL)  
 634 AATGGGGACT GGGAAAGCTT TCATAACAGT GATTAGGCAG TTGACCATGT TCGAACACACC 693  
 694 TCCCCGTCTA TACCAGGGAA CACAAAAATT GACTGGGCTA AGCCTGGACT TTCAAGGGAA 753  
     GCCTGGACT GTC (CBE-P53)  
 754 ATATGAAAAA CTGAGAGCAA AACAAAAGAC ATGGTTAAAA GGCAACCAGA ACATTGTGAG 813  
     ATTTTCTGA TTGGTTAAAA GT (NFE1)  
 814 CCTTCAAAGC AGCAGTGCCC CTCAGCAGGG ACCCTGAGGC ATTTGCCTT AGGAAGGCCA 873  
     G ACCCTGAGGC T (KTF.1-CS)  
 874 GTTTCTTAA GGAATCTTAA GAAACTCTTG AAAGATCATG AATTTAACCC ATTAAAGTA 933  
 934 TAAAACAAAT ATGCGATGCA TAATCAGTT AGACATGGGT CCCAATTAA TAAAGTCAGG 993  
     (PRE-1ysozyme) AGGCCGT  
 994 CATAACAAGGA TAACGTGTCC CAGCTCCGGA TAGGTCAGAA ATCATTAGAA ATCACTGTGT 1053  
     GATCCAAGGA GCAGAAGTTC CAGCTATGGT CAG (GRE-hMT) GG TACACTGTGT  
 1054 CCCCATCCTA ACTTTTCAG AATGATCTGT CATAGCCCTC ACACACAGGC CCGATGTGTC 1113  
     CCT  
 1114 TGACCTACAA CCACATCTAC AACCCAAAGTG CCTCAACCCT TGTTAACGTG TCATCTCAGT 1173

FIG. 1A

FIG. 1B

2494 ATTCCAGGAG GTGGGGACTG CAGGGAGTGG GGACGCCTGGG GCTGAGCGGG TGCTGAAAGG 2553  
 CTGG GGAGCCTGGG GA (AP.2-SV40)

2554 CAGGAAGGTG AAAAGGGCAA GGCTGAAGCT GCCCAGATGT TCAGTGTGT TCACGGGCT 2613

2614 GGGAGTTTC CGTTGCTTCC TGTGAGCCTT TTTATCTTTT CTCTGCTTGG AGGAGAAGAA 2673  
 CT CGTTGCTTCG AG (HSTF-hsp70)

2674 GTCTATTC A TGAAGGGATG CAGTTTCATA AAGTCAGCTG TTAAAATTCC AGGGTGTGCA 2733  
 A

2734 TGGGTTTCC TTCACGAAGG CCTTTATTAA ATGGGAATAT AGGAAGCGAG CTCATTTCC 2793  
 TGGGTTTTG (SBF.yeast)

2794 AGGCCGTTAA TTCACGGAAG AAGTGACTGG AGTCTTTCTT TTCAATGTCTT CTGGGCAACT 2853

2854 ACTCAGCCCT GTGGTGGACT TGGCTTATGC AAGACGGTCG AAAACCTTGG AATCAGGAGA 2913

2914 CTCGGTTTTC TTTCTGGTTC TGCCATTGGT TGGCTGTGCG ACCGTGGGCA AGTGTCTCTC 2973  
 C TTTCTGGTTT TGCAG (NF.1-bithorax)  
 (NF-MHCII/)CCATTGGT T

2974 CTTCCCTGGG CCATAGTCTT CTCTGCTATA AAGACCCTTG CAGCTCTCGT GTTCTGTGAA 3033

3034 CACTCCCTG TGATTCTCTG TGAGGGGGGA TGTTGAGAGG GGAAGGGAGGC AGAGCTGGAG 3093

3094 CAGCTGAGCC ACAGGGGAGG TGGAGGGGGGA CAGGAAGGCA GGCAGAACCT GGGTGCTCCA 3153

3154 TCAGTCCTCA CTGATCACGT CAGACTCCAG GACCGAGAGC CACAATGCTT CAGGAAAGCT 2943

2944 CAATGAACCC AACAGCCACA TTTTCCTTCC CTAAGCATAG ACAATGGCAT TTGCCAATAA 3273

3274 CCAAAAAGAA TGCAAGAGACT AACTGGTGGT AGCTTTGCC TGGCATTCAA AAACCTGGGCC 3333  
 GAAGTGACT AACTG (PEA.1-Polyoma)

3334 AGAGCAAGTG GAAAATGCCA GAGATTGTTA AACTTTTAC CCTGACCAGC ACCCCACGCA 3393

3394 GCTCAGCAGT GACTGCTGAC AGCACGGAGT GACCTGCAGC GCAGGGGAGG AGAAGAAAAA 3453  
 C AGGTAGAGT GACCTG (ERE.2-Vitel.)

3454 GAGAGGGATA GTGTATGAGC AAGAAAGACA GATTCTTCA AGGGCAGTGG GAATTGACCA 3513

3514 CAGGGATTAT AGTCCACGTG ATCCTGGGTT CTAGGAGGCA GGGCTATATT GTGGGGGGAA 3573  
 (GRE-FLV) CGGGATAC CGAGAGAACAA GGGCTATAGG

3574 AAAATCAGTT CAAGGGAAAGT CGGGAGACCT GATTCTTAAT ACTATATTTT TCCTTACAA 3633  
 GAGACC (SSRE)

3634 GCTGAGTAAT TCTGAGCAAG TCACAAGGTA GTAAGTGAGG CTGTAAGATT ACTTAGTTTC 3693  
 (ICS-MTII/ HLA-DR/)AGTTTC

3694 TCCTTATTAG GAACTTTT TCTCTGTGGA GTTAGCAGCA CAAGGGCAAT CCCGTTCTT 3753  
 TCCTCT

3754 TTAACAGGAA GAAAACATTG CTAAGAGTAA AGCCAAACAG ATTCAAGCCT AGGTCTTGCT 3813

3814 GACTATATGA TTGGTTTTT GAAAATCAT TTCAGCGATG TTTACTATCT GATTCAAGAAA 3873

FIG.1C

3874 ATGAGACTAG TACCCTTGG TCAGCTGTAA ACAAACACCC ATTTGT~~AAT~~ GTCTCAAGTT 3933  
GG TCA (1/2 ERE)

3934 CAGGCTTAAC TGCAGAACCA ATCAAATAAG AATAGAATCT TTAGAGCAAA CTGTGTTCT 3993

3994 CCACTCTGGA GGTGAGTCTG CCAGGGCAGT TTGGAAATAT TTACTTCACA AGTATTGACA 4053

4054 CTGTTGTTGG TATTAACAAC ATAAAGTTGC TCAAAGGCAA TCATTATTC AAGTGGCTTA 4113

4114 AAGTTACTTC TGACAGTTTT GGTATATTAA TTGGCTATTG CCATTTGCTT TTTGTTTTT 4173  
(NF.1-HCMV) TTGGCTATTG GCCA CTTT

4174 CTCTTGCGGT TTATTAATGT AAAGCAGGGA TTATTAACCT ACAGTCCAGA AAGCCTGTGA 4233  
CTCTTT (ISGF2)

4234 ATTTGAATGA GGAAAAAATT ACATTTTGT TTTTACCACC TTCTAACTAA ATTTAACATT 4293  
(Zn binding)-----

4294 TTATTCCATT GCGAATAGAG CCATAAACTC AAAGTGGTAA TAACAGTACC TGTGATTTG 4353

4354 TCATTACCA TAGAAATCAC AGACATTTA TACTATATTA CAGTTGTTGC AGATACGTTG 4413  
(CAP-ga10) ATTTA TTCCATGTCA CACTTTCGC A

4414 TAAGTGAAT ATTATACTC AAAACTACTT TGAAATTAGA CCTCCGTCTG GATCTGTTT 4473  
TTACTC A (AP-1)

4474 TTAACATATT AATAAAACAT GTTAAAATT TTGATATTTT GATAATCATA TTTCATTATC 4533  
GAT GTTAAAAT (PRL-FPII)

4534 ATTTGTTCC TTTGTAATCT ATATTTATA TATTTGAAAA CATCTTCTG AGAAGAGTTC 4593  
(GRE-MURFV) TGTTTTCTG AGAACATCAG

4594 CCCAGATTC ACCAATGAGG TTCTGGCAT GCACACACAC AGAGTAAGAA CT~~ATTTAGA~~ 4653  
CCAGATCTC ACCATCATTAT (nGRE) CACACACAC A (CACA)  
CTCTGG GGACAC AGAGTAGGG (AP.1-TGF $\beta$ )

4654 GGCTAACATT GACATTGGTG CCTGAGATGC AAGACTGAAA TTAGAAAGTT CTCCCAAAGA 4713  
(GC2) GATGCT GATGGATAAT TTAGAAGCTT CTCCCACA

4714 TACACAGTTG TTTAAAGCT AGGGGTGAGG GGGGAAATCT GCCGCTCTA TAGGAATGCT 4773  
(PEA.3)AGGAA GGT

4774 CTCCCTGGAG CCTGGTAGGG TGCTGTCCTT GTGTTCTGGC TGGCTGTTAT TTTCTCTGT 4833  
CTC (SSRE) MIR Repeat Region

4834 CCCTGCTACG TCTAAAGGA CT~~TGTTGG~~ TCTCCAGTTC CTAGCATAGT GCCTGGCACA 4893  
GGA CTTGTTGTT CT (GRE- $r$ TAT-II) TGGGCACA  
GCAAAAGGA TCTATTGG A (GRE-MMTV)

4894 GTGCAGGTTC TCAATGAGTT TGCAGAGTGA ATGGAAATAT AAACTAGAAA TATATCCTTG 4953  
GTGCCAA (NF-1) (HNF-1)C TGTGAAATAT TAACTAAA

4954 TTGAAATCAG CACACCAGTA GTCCTGGTGT AAGTGTGTGT ACGTGTGTGT GTGTGTGT 5013

FIG.1D

5014 GTGTGTGT AAAACCAGGT GGAGATATAG GAACTATTAT TGGGGTATGG GTGCATAAAT 5073  
cat/reverse cat box

5074 TGGGATGTTTC TTTTAAAAA GAAACTCCAA ACAGACTTCT GGAAGGTTAT TTTCTAAGAA 5133  
(1/2GRE)TGTTTC T (HSTF) GAAACTTCT GGAATATTCC CGAACTTTC  
C CTTTAGAAA GGA---CAA ACAGAATG(nGRE-Pr1)

5134 TCTTGCTGGC AGCGTGAAGG CAACCCCCCT GTGCACAGCC CCACCCAGCC TCACGTGGCC 5193  
(1/2 TRE)AGG CAA T-CC CCAGGCTCCC -CAG(AP.2-SV40)  
GGAGAGCC CC (NF-KB)

5194 ACCTCTGTCT TCCCCCATGA AGGGCTGGCT CCCCAGTATA TATAAACCTC TCTGGAGCTC 5253  
tata box GGTC TC (SSRE)

5254 GGGCATGAGC CAGCAAGGC\*C\* ACCCATCCAG GCACCTCTCA GCACAGC 5300  
Start Sites

## FIG.1E

1 ATC TTTGTTCA GTTACCTCAGG GCTATTATGA 33  
34 AATGAAATGA GATAACCAAT GTGAAAGTCC TATAAACTGT ATAGCCTCCA TTGGATGTA 93  
94 TGTCTTGCG AGGATGATAA AGAACAGGA AGAAGGAGTA TCCACGTTAG CCAAGTGTCC 153  
154 AGGCTGTGTC TGCTCTTATT TTAGTGACAG ATGTTGCTCC TGACAGAAGC TATTCTTCAG 213  
214 GAAACATCAC ATCCAATATG GTAAATCCAT CAAACAGGAG CTAAGAAACA GGAATGAGAT 273  
274 GGGCACTTGC CCAAGGAAAA ATGCCAGGAG AGCAAATAAT GATGAAAAT AAACCTTCC 333  
334 CTTTGTCCCC AATTCAGGA AAAATGATG AGGACCAAAA TCAATGAATA AGGAAAACAG 393  
394 CTCAGAAAAA AGATGTTTCC AAATTGGTAA TTAAGTATTG GTTCTTGAG AAGAGACCTC 453  
454 CATGTGAGCT TGATGGAAA ATGGGAAAA CGTCAAAAGC ATGATCTGAT CAGATCCCAA 513  
514 AGTGGATTAT TATTTAAAA ACCAGATGGC ATCACTCTGG GGAGGCAAGT TCAGGAAGGT 573  
574 CATGTTAGCA AAGGACATAA CAATAACAGC AAAATCAAAA TTCCGCAAAT GCAGGAGGAA 633  
634 AATGGGGACT GGGAAAGCTT TCATAACAGT GATTAGGCAG TTGACCATGT TCGAACACCC 693  
694 TCCCCGTCTA TACCAGGGAA CACAAAATT GACTGGCTA AGCCTGGACT TTCAAGGGAA 753  
754 ATATGAAAAA CTGAGAGCAA AACAAAAGAC ATGGTTAAAA GGCAACCAGA ACATTGTGAG 813  
814 CCTTCAAAGC AGCAGTGCCC CTCAGCAGGG ACCCTGAGGC ATTTGCCTTT AGGAAGGCCA 873  
874 GTTTCTTAA GGAATCTTAA GAAACTCTTG AAAGATCATG AATTTAACCC ATTAAAGTA 933  
934 TAAAACAAAT ATGCGATGCA TAATCAGTT AGACATGGGT CCCAATTAA TAAAGTCAGG 993  
994 CATAACAAGGA TAACGTGTCC CAGCTCCGGAA TAGGTCAGAA ATCATTAGAA ATCACTGTGT 1053  
1054 CCCCATCCTA ACTTTTCAG AATGATCTGT CATAGCCCTC ACACACAGGC CCGATGTGTC 1113  
1114 TGACCTACAA CCACATCTAC AACCCAAAGTG CCTCAACCCT TGTTAACGTG TCATCTCAGT 1173  
1174 AGGTCCCATT ACAAAATGCCA CCTCCCCGTG GCAGCCCATC CCGCTCCACA GGAAGTCTCC 1233  
1234 CCACTCTAGA CTTCTGCATC ACGATGTTAC AGCCAGAAGC TCCGTGAGGG TGAGGGTCTG 1293  
1294 TGTCTTACAC CTACCTGTAT GCTCTACACC TGAGCTCACT GCAACCTCTG CCTCCAGGT 1353  
1354 TCAAGCAATT CTCCGTCTC AGCCTCCCGC GTAGCTGGGA CTACAGGCGC ACGCCCGGCT 1413  
1414 AATTTTGTA TTGTTAGTAG AGATGGGGTT TCACCATATT AGCCCGGCTG GTCTTGAAC 1473

FIG.2A

1474 CCTGACCTCA GGTGATCCAC CCACCTCAGC CTCCTAAAGT GCTGGGATTA CAGGCATGAG 1533  
1534 TCACCGCGCC CGGCCAAGGG TCAGTGTTA ATAAGGAATA ACTTGAATGG TTTACTAAAC 1593  
1594 CAACAGGGAA ACAGACAAAA GCTGTGATAA TTTCAGGGAT TCTTGGGATG GGGATGGTG 1653  
1654 CCATGAGCTG CCTGCCTAGT CCCAGACCAC TGGTCCTCAT CACTTCTTC CCTCATCCTC 1713  
1714 ATTTTCAGGC TAAGTTACCA TTTTATTACAT CATGCTTTG TGGTAAGCCT CCACATCGTT 1773  
1774 ACTGAAATAA GAGTATAACAT AACTAGTTC CATTGGGGC CATCTGTGTG TGTGTATAGG 1833  
1834 GGAGGAGGGC ATACCCCAGA GACTCCTGA AGCCCCGGC AGAGGTTCC TCTCCAGCTG 1893  
1894 GGGGAGCCCT GCAAGCACCC GGGGTCCCTGG GTGTCCCTGAG CAACCTGCCA GCCCGTGCCA 1953  
1954 CTGGTTGTT TGTTATCACT CTCTAGGGAC CTGTTGCTTT CTATTTCTGT GTGACTCGTT 2013  
2014 CATTCACTCCA GGCATTCACTT GACAATTAT TGAGTACTTA TATCTGCCAG ACACCAGAGA 2073  
2074 CAAAATGGTG AGCAAAGCAG TCACTGCCCT ACCTTCGTGG AGGTGACAGT TTCTCATGGA 2133  
2134 AGACGTGCAG AAGAAAATTA ATAGCCAGCC AACTTAAACC CAGTGCTGAA AGAAAGGAAA 2193  
2194 TAAACACCAT CTTGAAGAAT TGTGCGCAGC ATCCCTAAC AAGGCCACCT CCCTAGCGCC 2253  
2254 CCCTGCTGCC TCCATCGTGC CCGGAGGCC CCAAGCCCGA GTCTTCCAAG CCTCCTCCTC 2313  
2314 CATCAGTCAC AGCGCTGCAG CTGGCCTGCC TCGCTTCCCG TGAATCGTCC TGGTGCATCT 2373  
2374 GAGCTGGAGA CTCCTGGCT CCAGGCTCCA GAAAGGAAAT GGAGAGGGAA ACTAGTCTAA 2433  
2434 CGGAGAATCT GGAGGGGACA GTGTTCCCTC AGAGGGAAAG GGGCCTCCAC GTCCAGGAGA 2493  
2494 ATTCCAGGAG GTGGGGACTG CAGGGAGTGG GGACGCTGGG GCTGAGCGGG TGCTGAAAGG 2553  
2554 CAGGAAGGTG AAAAGGGCAA GGCTGAAGCT GCCCAGATGT TCAGTGTGT TCACGGGCT 2613  
2614 GGGAGTTTC CGTTGCTTCC TGTGAGCCTT TTTATCTTT CTCTGCTTGG AGGAGAAGAA 2673  
2674 GTCTATTCAGA TGAAGGGATG CAGTTCTATA AAGTCAGCTG TTAAAATTCC AGGGTGTGCA 2733  
2734 TGGGTTTCC TTCACGAAGG CCTTTATTTA ATGGGAATAT AGGAAGCGAG CTCATTTCC 2793  
2794 AGGCCGTTAA TTCACGGAAG AAGTGAATGG AGTCTTTCT TTCATGTCTT CTGGGCAACT 2853  
2854 ACTCAGCCCT GTGGTGGACT TGGCTTATGC AAGACGGTCG AAAACCTGG AATCAGGAGA 2913  
2914 CTCGGTTTC TTTCTGGTTC TGCCATTGGT TGGCTGTGCG ACCGTGGCA AGTGTCTCTC 2973  
2974 CTTCCCTGGG CCATAGTCTT CTCTGCTATA AAGACCCCTG CAGCTCTCGT GTTCTGTGAA 3033  
3034 CACTCCCTG TGATTCTCTG TGAGGGGGGA TGTTGAGAGG GGAAGGAGGC AGAGCTGGAG 3093

FIG.2B

3094 CAGCTGAGCC ACAGGGGAGG TGGAGGGGGA CAGGAAGGCA GGCAGAAGCT GGGTGCTCCA 3153  
3154 TCAGTCCTCA CTGATCACGT CAGACTCCAG GACCGAGAGC CACAATGCTT CAGGAAAGCT 2943  
2944 CAATGAACCC AACAGCCCACA TTTTCCTTCC CTAAGCATAG ACAATGGCAT TTGCCAATAA 3273  
3274 CCAAAAAGAA TGCAAGAGCT AACTGGTGGT AGCTTTGCC TGGCATTCAA AAACCTGGCC 3333  
3334 AGAGCAAGTG GAAAATGCCA GAGATTGTTA AACTTTCAC CCTGACCAGC ACCCCACGCA 3393  
3394 GCTCAGCAGT GACTGCTGAC AGCACGGAGT GACCTGCAGC GCAGGGGAGG AGAAGAAAAA 3453  
3454 GAGAGGGATA GTGTATGAGC AAGAAAGACA GATTCAATTCA AGGGCAGTGG GAATTGACCA 3513  
3514 CAGGGATTAT AGTCCACGTG ATCCTGGTT CTAGGAGGCA GGGCTATATT GTGGGGGGAA 3573  
3574 AAAATCAGTT CAAGGGAAGT CGGGAGACCT GATTCTAAT ACTATATTTT TCCTTACAA 3633  
3634 GCTGAGTAAT TCTGAGCAAG TCACAAGGTA GTAAGTGAGG CTGTAAGATT ACTTAGTTTC 3693  
3694 TCCTTATTAG GAACTCTTTT TCTCTGTGGA GTTAGCAGCA CAAGGGCAAT CCCGTTCTT 3753  
3754 TTAACAGGAA GAAAACATTG CTAAGAGTAA AGCCAAACAG ATTCAAGCCT AGGTCTTGCT 3813  
3814 GACTATATGA TTGGTTTTT GAAAAATCAT TTCAGCGATG TTTACTATCT GATTCAAGAAA 3873  
3874 ATGAGACTAG TACCCTTGG TCAGCTGAA ACAAACACCC ATTTGTAAT GTCTCAAGTT 3933  
3934 CAGGCTTAAC TGCAGAACCA ATCAAATAAG AATAGAATCT TTAGAGCAAA CTGTGTTCT 3993  
3994 CCACTCTGGA GGTGAGTCTG CCAGGGCAGT TTGGAAATAT TTACTTCACA AGTATTGACA 4053  
4054 CTGTTGTTGG TATTAACAAAC ATAAAGTTGC TCAAAGGCAA TCATTATTC AAGTGGCTTA 4113  
4114 AAGTTACTTC TGACAGTTTT GGTATATTTA TTGGCTATTG CCATTTGCTT TTGTTTTTT 4173  
4174 CTCTTGGGT TTATTAATGT AAAGCAGGGA TTATTAACCT ACAGTCCAGA AAGCCTGTGA 4233  
4234 ATTTGAATGA GGAAAAAATT ACGTTTTAT TTTTACCAAC TTCTAACTAA ATTTAACATT 4293  
4294 TTATTCCATT GCGAATAGAG CCATAAACTC AAAGTGGTAA TAAGAGTACC TGTGATTTG 4353  
4354 TCATTACCAA TAGAAATCAC AGACATTTA TACTATATTA CAGTTGTTGC AGGTACGTTG 4413  
4414 TAAGTGAAT ATTTATACTC AAAACTACTT TGAAATTAGA CCTCCTGCTG GATCTTGTTC 4473  
4474 TTAACATATT AATAAAACAT GTTTAAAATT TTGATATTT GATAATCATA TTTCATTATC 4533  
4534 ATTTGTTCC TTTGTAATCT ATATTTATA TATTTGAAAA CATCTTCTG AGAAGAGTTC 4593  
4594 CCCAGATTC ACCAATGAGG TTCTGGCAT GCACACACAC AGAGTAAGAA CTGATTTAGA 4653  
4654 GGCTAACATT GACATTGGTG CCTGAGATGC AAGACTGAAA TTAGAAAGTT CTCCCAAAGA 4713

FIG.2C

4714 TACACAGTTG TTTTAAAGCT AGGGGTGAGG GGGGAAATCT GCCGCTTCTA TAGGAATGCT 4773  
4774 CTCCCTGGAG CCTGGTAGGG TGCTGTCCTT GTGTTCTGGC TGGCTGTTAT TTTCTCTGT 4833  
4834 CCCTGCTACG TCTTAAAGGA CTTGTTGGA TCTCCAGTTC CTAGCATAGT GCCTGGCACA 4893  
4894 GTGCAGGTTC TCAATGAGTT TGCAGAGTGA ATGAAATAT AACTAGAAA TATATCTTG 4953  
4954 TTGAAATCAG CACACCAGTA GTCCTGGTGT AAGTGTGTGT ACGTGTGTGTGT GTGTGTGT5017  
5018 GTGTGTGTGT AAAACCAGGT GGAGATATAG GAACTATTAT TGGGGTATGG GTGCATAAAT 5077  
5078 TGGGATGTTTC TTTTAAAAAA GAAACTCCAA ACAGACTTCT GGAAGGTTAT TTTCTAAGAA 5137  
5138 TCTTGCTGGC AGCGTGAAGG CAACCCCCCT GTGCACAGCC CCACCCAGCC TCACGTGGCC 5197  
5198 ACCTCTGTCT TCCCCCATGA AGGGCTGGCT CCCCAGTATA TATAAACCTC TCTGGAGCTC 5257  
5258 GGGCATGAGC CAGCAAGGCC ACCCATCCAG GCACCTCTCA GCACAGC 5304

## FIG.2D

1 ATCTTGTT AGTTACCTC AGGGCTATT TGAAATGAAA TGAGATAACC  
51 AATGTGAAAG TCCTATAAAC TGTATAGCCT CCATTCGGAT GTATGTCTTT  
101 GGCAGGATGA TAAAGAATCA GGAAGAAGGA GTATCCACGT TAGCCAAGTG  
151 TCCAGGCTGT GTCTGCTCTT ATTTTAGTGA CAGATGTTGC TCCTGACAGA  
201 AGCTATTCTT CAGGAAACAT CACATCCAAT ATGGTAAATC CATCAAACAG  
251 GAGCTAAGAA ACAGGAATGA GATGGGCACT TGCCCAGGA AAAATGCCAG  
301 GAGAGCAAAT AATGATGAAA AATAAACTTT TCCCTTGTT TTTAATTCA  
351 GGAAAAAAATG ATGAGGACCA AAATCAATGA ATAAGGAAAA CAGCTCAGAA  
401 AAAAGATGTT TCCAAATTGG TAATTAAGTA TTTGTTCTT GGGAAAGAGAC  
451 CTCCATGTGA GCTTGATGGG AAAATGGAA AAACGTCAA AGCATGATCT  
501 GATCAGATCC CAAAGTGGAT TATTATTTA AAAACCAGAT GGCATCACTC  
551 TGGGGAGGCA AGTCAGGAA GGTCACTGTTA GCAAAGGACA TAACAATAAC  
601 AGCAAAATCA AAATCCGCA AATGCAGGAG GAAAATGGGG ACTGGGAAAG  
651 CTTTCATAAC AGTGATTAGG CAGTTGACCA TGTTCGAAC ACCTCCCCGT  
701 CTATACCAGG GAACACAAAA ATTGACTGGG CTAAGCCTGG ACTTTCAAGG  
751 GAAATATGAA AAAC TGAGAG CAAAACAAAA GACATGGTTA AAAGGCAACC  
801 AGAACATTGT GAGCCTCAA AGCAGCAGTG CCCCTCAGCA GGGACCCCTGA  
851 GGCATTTGCC TTTAGGAAGG CCAGTTTCT TAAGGAATCT TAAGAAACTC  
901 TTGAAAGATC ATGAATTAA ACCATTTAA GTATAAAACA AATATGCGAT  
951 GCATAATCAG TTTAGACATG GGTCCAATT TTATAAGTC AGGCATACAA  
1001 GGATAACGTG TCCCAGCTCC GGATAGGTCA GAAATCATT GAAATCACTG  
1051 TGTCCCCATC CTAACTTTT CAGAATGATC TGTCAAGCC CTCACACACA  
1101 GGCCCGATGT GTCTGACCTA CAACCACATC TACAACCCAA GTGCCTCAAC  
1151 CATTGTTAAC GTGTCACTC AGTAGGTCCC ATTACAAATG CCACCTCCCC  
1201 TGTGCAGCCC ATCCCGCTCC ACAGGAAGTC TCCCCACTCT AGACTTCTGC  
1251 ATCACGATGT TACAGCCAGA AGCTCCGTGA GGGTGAGGGT CTGTGTCTTA

FIG.3A

1301 CACCTACCTG TATGCTCTAC ACCTGAGCTC ACTGCAACCT CTGCCTCCCA  
1351 GGTTCAAGCA ATTCTCCTGT CTCAGCCTCC CGCGTAGCTG GGACTACAGG  
1401 CGCACGCCCG GCTAATTTT GTATTGTTAG TAGAGATGGG GTTTCACCAT  
1451 ATTAGCCCGG CTGGTCTTGA ACTCCTGACC TCAGGTGATC CACCCACCTC  
1501 AGCCTCCTAA AGTGCTGGGA TTACAGGCAT GAGTCACCGC GCCCGGCCAA  
1551 GGGTCAGTGT TTAATAAGGA ATAACCTGAA TGGTTTACTA AACCAACAGG  
1601 GAAACAGACA AAAGCTGTGA TAATTCAGG GATTCTTGGG ATGGGGAATG  
1651 GTGCCATGAG CTGCCCTGCCT AGTCCCAGAC CACTGGTCCT CATCACTTTC  
1701 TTCCCTCATC CTCATTTCA GGCTAAGTTA CCATTTTATT CACCATGCTT  
1751 TTGTGGTAAG CCTCCACATC GTTACTGAAA TAAGAGTATA CATAAACTAG  
1801 TTCCATTGG GGCCATCTGT GTGTGTGTAT AGGGGAGGAG GGCATACCCC  
1851 AGAGACTCCT TGAAGCCCCC GGCAGAGGTT TCCTCTCCAG CTGGGGGAGC  
1901 CCTGCAAGCA CCCGGGGTCC TGGGTGTCCCT GAGCAACCTG CCAGCCCGTG  
1951 CCACTGGTTG TTTTGTATC ACTCTCTAGG GACCTGTTGC TTTCTATTTC  
2001 TGTGTGACTC GTTCATTATC CCAGGCATTG ATTGACAATT TATTGAGTAC  
2051 TTATATCTGC CAGACACCAAG AGACAAAATG GTGAGCAAAG CAGTCACTGC  
2101 CCTACCTTCG TGAGGTGAC AGTTTCTCAT GGAAGACGTG CAGAAGAAAA  
2151 TTAATAGCCA GCCAACTTAA ACCCAGTGCT GAAAGAAAGG AAATAAACAC  
2201 CATCTTGAAG AATTGTGCGC AGCATCCCTT ACAAGGCCA CCTCCCTAGC  
2251 GCCCCCTGCT GCCTCCATCG TGCCCGGAGG CCCCCAAGCC CGAGTCTTCC  
2301 AAGCCTCCTC CTCCATCACT CACAGCGCTG CAGCTGGCCT GCCTCGCTTC  
2351 CCGTGAATCG TCCTGGTGCA TCTGAGCTGG AGACTCCTTG GCTCCAGGCT  
2401 CCAGAAAGGA AATGGAGAGG GAAACTAGTC TAACGGAGAA TCTGGAGGGG  
2451 ACAGTGTTC CTCAGAGGGA AAGGGGCCTC CACGTCCAGG AGAATTCCAG  
2501 GAGGTGGGGA CTGCAGGGAG TGGGGACGCT GGGGCTGAGC GGGTGCTGAA  
2551 AGGCAGGAAG GTGAAAAGGG CAAGGCTGAA GCTGCCAGA TGTTCACTGT  
2601 TGTTCACGGG GCTGGGAGTT TTCCGTTGCT TCCTGTGAGC CTTTTATCT

FIG.3B

2651 TTTCTCTGCT TGGAGGGAGAA GAAGTCTATT TCATGAAGGG ATGCAGTTTC  
2701 ATAAAGTCAG CTGTTAAAAT TCCAGGGTGT GCATGGGTTT TCCTTCACGA  
2751 AGGCCTTTAT TTAATGGGAA TATAGGAAGC GAGCTCATTT CCTAGGCCGT  
2801 TAATTCACCGG AAGAAGTGAC TGGAGTCCTT TCTTCATGT CTTCTGGGCA  
2851 ACTACTCAGC CCTGTGGTGG ACTTGGCTTA TGCAAGACGG TCGAAAACCT  
2901 TGGAATCAGG AGACTCGGTT TTCTTCTGG TTCTGCCATT GGTTGGCTGT  
2951 GCGACC GTGG GCAAGTGTCT CTCCCTCCCT GGGCCATAGT CTTCTCTGCT  
3001 ATAAAGACCC TTGCAGCTCT CGTGTCTGT GAACACTTCC CTGTGATTCT  
3051 CTGTGAGGGGG GGATGTTGAG AGGGGAAGGA GGCAAGAGCTG GAGCAGCTGA  
3101 GCCACAGGGGG AGGTGGAGGG GGACAGGAAG GCAGGCAGAA GCTGGGTGCT  
3151 CCATCAGTCC TCACTGATCA CGTCAGACTC CAGGACCGAG AGCCACAATG  
3201 CTTCAAGGAAA GCTCAATGAA CCCAACAGCC ACATTTCCCT TCCCTAAGCA  
3251 TAGACAATGG CATTGCCAA TAACCAAAAA GAATGCAGAG ACTAACTGGT  
3301 GGTAGCTTTT GCCTGGCATT CAAAAACTGG GCCAGAGCAA GTGGAAAATG  
3351 CCAGAGATTG TAAACTTTT CACCCCTGACC AGCACCCCCAC GCAGCTCAGC  
3401 AGTGACTGCT GACAGCACGG AGTGACCTGC AGCGCAGGGG AGGAGAAGAA  
3451 AAAGAGAGGGG ATAGTGTATG AGCAAGAAAG ACAGATTCA TCAAGGGCAG  
3501 TGGGAATTGA CCACAGGGAT TATAGTCCAC GTGATCCTGG GTTCTAGGAG  
3551 GCAGGGCTAT ATTGTGGGGG GAAAAAAATCA GTTCAAGGGAA AGTCGGGAGA  
3601 CCTGATTCT AATACTATAT TTTCCCTTA CAAGCTGAGT AATTCTGAGC  
3651 AAGTCACAAG GTAGTAACTG AGGCTGTAAG ATTACTTAGT TTCTCCTTAT  
3701 TAGGAACCTCT TTTCTCTGT GGAGTTAGCA GCACAAGGGC AATCCCCTT  
3751 CTTTAACAG GAAGAAAACA TTCCTAAGAG TAAAGCCAAA CAGATTCAAG  
3801 CCTAGGTCTT GCTGACTATA TGATTGGTTT TTTGAAAAAT CATTTCAGCG  
3851 ATGTTTACTA TCTGATTCAAG AAAATGAGAC TAGTACCCCTT TGGTCAGCTG  
3901 TAAACAAACA CCCATTGTA AATGTCTCAA GTTCAGGCTT AACTGCAGAA  
3951 CCAATCAAAT AAGAATAGAA TCTTAGAGC AACTGTGTT TCTCCACTCT

FIG.3C

4001 GGAGGTGAGT CTGCCAGGGC AGTTTGGAAA TATTACTTC ACAAGTATTG  
4051 ACACTGTTGT TGGTATTAAC AACATAAAAGT TGCTCAAAGG CAATCATTAT  
4101 TTCAAGTGGC TTAAAGTTAC TTCTGACAGT TTTGGTATAT TTATTGGCTA  
4151 TTGCCATTG CTTTTGTTT TTTCTTTG GGTTTATTAA TGAAAGCAG  
4201 GGATTATTAA CCTACAGTCC AGAAAGCCTG TGAATTGAA TGAGGAAAAA  
4251 ATTACATTTC TGTTTTACC ACCTCTAAC TAAATTAAAC ATTTTATTCC  
4301 ATTGCGAATA GAGCCATAAA CTCAAAGTGG TAATAACAGT ACCTGTGATT  
4351 TTGTCATTAC CAATAGAAAT CACAGACATT TTACTATA TTACAGTTGT  
4401 TGCAAGATAAG TTGTAAGTGA AATATTATA CTCAAAACTA CTTTGAAATT  
4451 AGACCTCCTG CTGGATCTTGT TTTTAACAT ATTAATAAAA CATGTTAAA  
4501 ATTTGATAT TTTGATAATC ATATTTCATT ATCATTGTGTT TCCTTGAA  
4551 TCTATATTTC ATATATTGA AAACATCTT CTGAGAAGAG TTCCCCAGAT  
4601 TTCACCAATG AGGTTCTTGG CATGCACACA CACAGAGTAA GAACTGATT  
4651 AGAGGCTAAC ATTGACATTG GTGCCTGAGA TGCAAGACTG AAATTAGAAA  
4701 GTTCTCCCAA AGATACACAG TTGTTTAAA GCTAGGGGTG AGGGGGGAAA  
4751 TCTGCCGCTT CTATAGGAAT GCTCTCCCTG GAGCCTGGTA GGGTGCTGTC  
4801 CTTGTGTTCT GGCTGGCTGT TATTTTCTC TGCCCTGCT ACGTCTTAAA  
4851 GGACTTGTGTT GGATCTCCAG TTCCTAGCAT AGTGCCTGGC ACAGTGCAGG  
4901 TTCTCAATGA GTTGAGAG TGAATGGAAA TATAAACTAG AAATATATCC  
4951 TTGTTGAAAT CAGCACACCA GTAGTCCTGG TGTAAGTGTG TGTACGTGTG  
5001 TGTGTGTGTG TGTGTGTGTG TGTAACACCA GGTGGAGATA TAGGAACTAT  
5051 TATTGGGGTA TGGGTGCATA AATTGGGATG TTCTTTTAA AAAGAAACTC  
5101 CAAACAGACT TCTGGAAGGT TATTTCTAA GAATCTTGCT GGCAGCGTGA  
5151 AGGCAACCCC CCTGTGCACA GCCCCACCCA GCCTCACGTG GCCACCTCTG  
5201 TCTTCCCCCA TGAAGGGCTG GCTCCCCAGT ATATATAAAC CTCTCTGGAG  
5251 CTCGGGCATG AGCCAGCAAG GCCACCCATC CAGGCACCTC TCAGCACAGC 5300

**FIG.3D**

1 AGAGCTTCCAGAGGAAGCCTCACCAAGCCTTGCAATGAGGTTCTGTGCACGTTGC 60  
61 TGCAGCTTGGCCTGAGATGCCAGCTGTCAGCTGCTGCTCTGGCCTGCCCTGGTGG 120  
121 GATGTGGGGCCAGGACAGCTAGCTCAGGAAGGCCAATGACCAGAGTGGCCGATGCCAG 180  
181 TATACTTCAGTGTGCCAGTCCAATGAATCCAGCTGCCAGAGCAGAGCCAGGCCATG 240  
241 TCAGTCATCCATAACTTACAGAGAGACAGCAGCACCCAACGCTTAGACCTGGAGGCCACC 300  
301 AAAGCTCGACTCAGCTCCCTGGAGAGCCTCCTCCACCAATTGACCTGGACCAGGCTGCC 360  
361 AGGCCCGAGGAGACCCAGGAGGGCTGCAGAGGGAGCTGGCACCCCTGAGGCGGGAGCGG 420  
421 GACCAGCTGGAAACCAAACAGAGAGTTGGAGACTGCCTACAGCAACCTCCTCCGAGAC 480  
481 AAGTCAGTTCTGGAGGAAGAGAAGAAGCGACTAAGGCAAGAAAATGAGAATCTGCCAGG 540  
541 AGGTTGGAAAGCAGCAGCCAGGAGGTAGCAAGGCTGAGAAGGGGCCAGTGTCCCCAGACC 600  
601 CGAGACACTGCTGGCTGTGCCACCAAGGCTCCAGAGAAG

(exon #2) TT TCT ACG TGG AAT TTG GAC

661 ACT TTG GCC TTC CAG GAA CTG AAG TCC GAG CTA ACT GAA GTT CCT GCT TCC CGA ATT TTG 720  
721 AAG GAG AGC CCA TCT GGCT AT CTC AGG AGT GGA GAG GGA GAC ACCG

(intron #2)  
gtatgaagttaagttcttcccttttgccccacgtggctttattcatgtcttagtgctgtgttcagagaa  
tcagtataggtaaatgcccacccacggggaaattaacttccctgggagcagaggggaggggagga  
qaagaggaacagaactctctctctctgttacccttgt-----Intron II - 3 kb-----

FIG. 3E

tggctctgccaaggcttcgcatgtatccatttgtttggaaagattatggattaaagtggcttcgtt  
ctttctgaatttacccag

(exon #3) GA TGT GGA GAA CTA 780

781	GTT	TGG	GTA	GGA	GAG	CCT	CTC	ACG	CTG	AGA	ACA	GCA	GAA	ACA	ATT	ACT	GGC	AAG	TAT	GGT	840
841	GTT	TGG	ATG	CGA	GAC	CCC	AAG	CCC	ACC	TAC	CCC	TAC	ACC	GAG	ACC	ACG	TGG	AGA	ATC	900	
901	GAC	ACA	GTT	GGC	ACG	GAT	GTC	CGC	CAG	GAT	GTT	GAG	TAT	GAC	CTC	ATC	AGC	CAG	TTT	ATG	960
961	CAG	GGC	TAC	CCT	TCT	AAG	GTT	CAC	ATA	CTG	CCT	AGG	CCA	CTG	GAA	AGC	ACG	GGT	GCT	GTT	1020
1021	GTT	TAC	TCG	GGG	AGC	CTC	TAT	TTC	CAG	GGC	GCT	GAG	TCC	AGA	ACT	GTC	ATA	AGA	TAT	GAG	1080
1081	CTG	AAT	ACC	GAG	ACA	GTG	AAG	GCT	GAG	AAG	GAA	ATC	CCT	GGA	GCT	TAC	CAC	GGA	CAG	1140	
1141	TTC	CCG	TAT	TCT	TGG	GGT	GGC	TAC	AGC	GAC	ATT	GAC	TTG	GCT	GAT	GAA	GCA	GGC	CTC	1200	
1201	TGG	GTC	ATT	TAC	AGC	GGT	AAA	GAT	GAG	GCC	ATT	GTC	CTC	TCC	AAA	CTG	AAC	CCA	1260		
1261	GAG	AAT	CTG	GAA	CTC	GAA	CAA	ACC	TGG	GAG	ACA	AAC	ATC	CCT	AAG	CAG	TCA	GTC	GCC	AAT	1320
1321	GCC	TTC	ATC	ATC	TGT	GGC	ACC	TTG	TAC	ACC	GTC	AGC	TAC	ACC	TCA	GCA	GAT	GCT	ACC	1380	
1381	GTC	AAC	TTT	GCT	TAT	GAC	ACA	GGC	ACA	GGT	ATC	AGC	AAG	ACC	CTG	ACC	ATC	CCA	TTC	AAG	1440
1441	AAC	CGC	TAT	AAG	TAC	AGC	AGC	ATG	ATT	GAC	TAC	AAC	CCC	CTG	GAG	AAG	CTC	TTT	GCC	1500	
1501	TGG	GAC	AAC	TTG	AAC	ATG	GTC	ACT	TAT	GAC	ATC	AAG	CTC	TCC	AAG	ATG					

1561	AAG	CTG	TAC	AGG	CAA	TGG	CAG	AAG	GAG	ATG	CTC	AGG	GCT	CCT	GGG	GGG	AGC	AGG	CTG	AAG	1620	
1621	GGA	GAG	CCA	GCC	GCC	GGC	AGC	AGC	AGC	TAA	CTA	TTT	CCA	AGT	TTT	CAT	TAA	TCC	1680			
1681	AGA	AGG	ATG	AAC	ATG	GTC	ACC	ATC	ATC	TTC	AGG	AAT	TGT	AGT	CTG	AGG	GCG	TAG	ACA	1740		
1741	ATT	TCA	TAT	AAA	TAT	CCT	TCT	TCT	GTC	AGC	ATT	TAT	GGG	ATG	TTT	AAT	GAC	ATA	1800			
1801	GTT	CAA	GTT	TTC	TGA	TTT	GGG	GCA	AAA	GCT	GTA	AGG	CAT	AAT	AGT	CTT	TTC	CTG	AAA	1860		
1861	ACC	ATT	GCT	CTT	GCA	TGT	TAC	ATG	GTT	ACC	ACA	AGC	CAC	AAT	AAA	AAG	CAT	AAC	TTC	TAA	1920	
1921	AGG	AAG	CAG	AAT	AGC	TCC	TCT	GGC	CAG	CAT	CGA	ATA	TAA	GTA	AGA	TGC	ATT	TAC	TAC	AGT	1980	
1981	TGG	CTT	CTA	ATG	CTT	CAG	ATA	GAA	TAC	AGT	TGG	GTC	TCA	CAT	AAC	CCT	TAC	ATT	GTG	AAA	2040	
2041	TAAT	TTT	CTT	ACC	CAA	CGT	TCT	CTT	CCT	TGA	ACT	TTG	TGG	CTT	AAG	TGA	TGT	GAT	TGC	AGG	ATG	2160
2101	AGG	ATA	TAG	ATT	CCA	ACC	ATC	AGG	TTA	TTC	CTT	CAG	TTT	GAA	TGT	GAT	TGC	AGG	ATG			

FIG.3F

2161 TTA AAG GTG TGT GTG TGT GTG TGT GTG TAA CTG AGA GGC TTG TGC CTG GTT TTG 2220  
2221 AGG TGC TGC CCA GGA TGA CGC CAA GCA AAT AGC GCA TCC ACA CTT TCC CAC CTC CAT CTC 2280  
2281 CTG GTG CTC TCG GCA CTA CCG GAG CAA TCT TTC CAT CTC TCC CCT GAA CCC ACC CTC TAT 2340  
2341 TCA CCC TAA CTC CAC TTC AGT TTG ATT TTG TTT TTT TTT TTT TTT TGA 2400  
2401 GAT GGG GTC TCG CTC TGT CAC CCA GGC TGG AGT GCA GTG GCA CGA TCT CGG CTC ACT GCA 2460  
2461 AGT TCC GCC TCC CAG GTT CAC ACC ATT CTC CTG CCT CAG CCT CCC AAG TAG CTG GGA CTA 2520  
2521 CAG GCA CCT GCC ACC ACG CCT GGC TAA TTT TTT TTT CCA GTG AAG ATG GGT TTC ACC 2580  
2581 ATG TTA GCC AGG ATG GTC TCG ATC TCC TGA C TTG ATC CAC CCA CCT TGG CCT CCC AAA 2640  
2641 GTG CTG GGA TTA CAG GCG TGA GCC ACC ACGC CCA GCC CCT CCA CTT CAG TTT TTA TCT GTC 2700  
2701 ATC AGG GGT ATG AAT TTT ATA AGC CAC ACC TCA GGT GGA GAA AGC TTG ATG CAT AGC TTG 2760  
2761 AGT ATT CTA TAC TGT 2776

FIG.3G

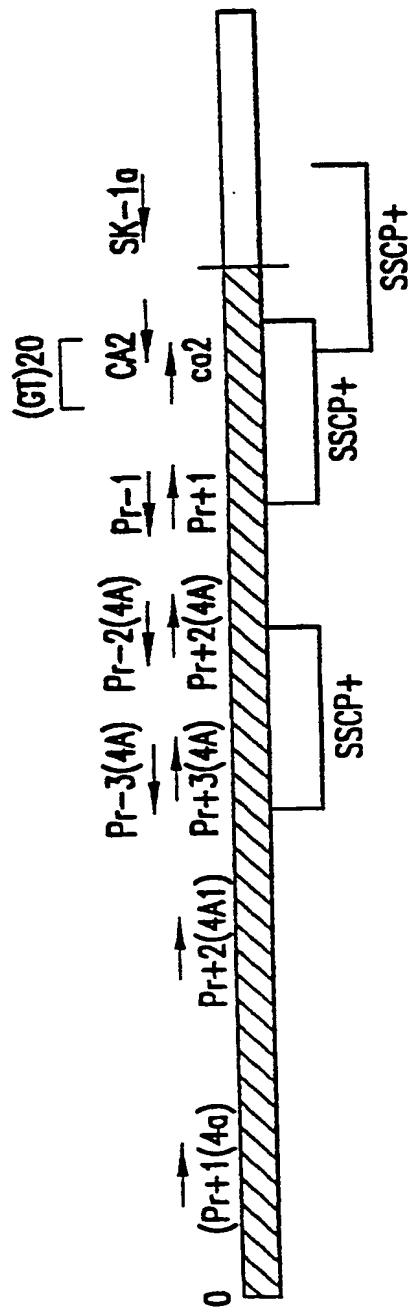


FIG. 4

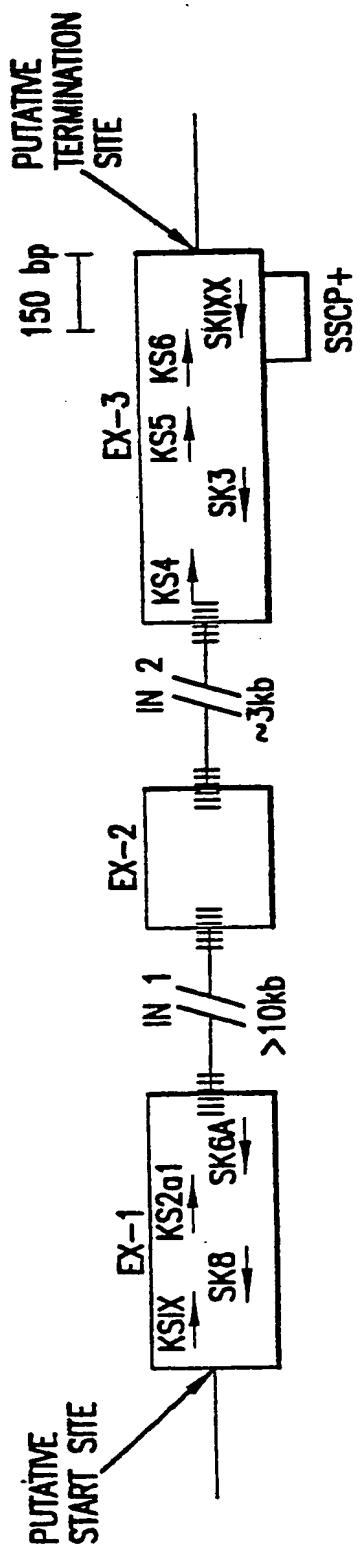


FIG. 5

TIGR	-TGAVVYSGS	LYFQGAESRT	VIRYELNTET	VAEKEIPGA	GYHGQFPYSW	GGYTDIDLAV	59	
ym08h12.r1	.....	.....	.....	--RFDLKTET	IJKTRSLDYA	GYNMYYHAW	GHSDIDLMV	38
1B426bAMZ	GTGQWVYNGS	IYFNKFQSHI	IIRFDLKTTET	IJKTRSLDYA	GYNMYYHAW	GGHSDIDLMV	60	
ranofm	GAGVVVHNNN	LYNCFNSHD	MCRASL-TSG	WYQKKPLLNA	LFNNRFSYAG	TMFQDMDFSS	59	
Consensus	..G. WV.....	.Y.....S...	..R..L..TET	.....L..A	GYNIN...YAW	GG..DIDL.V	60	

TIGR	DEAGLWIYS	TDEAKGAIWL	SKLNPNEL	EQTWETNIRK	QSVANAFIIC	GTLTYVSSYT	119
ym08h12.r1	DESGLWAWYA	TNQNAGNIVW	SRDPVSLQT	LQTWNTSYPK	RXPGXAFIIC	GTCYVTNGY-	97
1B426bAMZ	DENGLWAWYA	TNQNAGNIVI	SKLPVSLQI	LQTWNTSYPK	RSAGEAFIIC	GTLTYVNTNGYS	120
ranofm	DEKGLWIFT	TEKSAGKIVW	GKVNVATFTV	DNIWITTONQK	SDASNAFMIC	GVLYVTRSLG	119
Consensus	DE.GLW..Y.	T..AG.IV.	SKL.P..L...	.QTW.T..K	....AFIIC	GTLYVT..Y.	120

TIGR	SADATVNFAY	DTGTGISKTL	TIPFKNRYKY	SMIDYNPLE	KKLFAMDNLN	MVTDIKLS	178
ym08h12.r1	SGGTKWHYAY	QTNAST---	-----	-----	-----	-----	131
1B426bAMZ	GG-TKWHYAY	QTNASTYEYI	DIPFQNKYSH	ISMLDYNPKD	RALYAWNINGH	QTLYNVTLF	178
ranofm	PKMEEVFYMF	DTKTGKEGH	SLIMMEKMAEK	WHSLSYNSND	RKL YMFSEGY	LLHYDIAL-	177
Consensus	....V.YAY	.T.....	....I.....	....Y...	....DYNP...	....KL.....	178

**FIG.6**

1 AGA GCT TTC CAG AGG AAG CCT CAC CAA GCC TCT GCA ATG AGG TTC TTC TGT GCA CGT CGT 60  
61 TGC AGC TTT GGG CCT GAG ATG CCA GCT GTC CAG CTG CTT CTG GCC TGC CTG GTG TGG 120  
121 GAT GTG GGG GCC AGG ACA GCT CAG CTC AAG AAG GCC AAT GAC CAG AGT GGC CGA TGC CAG 180  
181 TAT ACC TTC AGT GTG GCC AGT CCC AAT GAA TCC AGC TGC CCA GAG CAG AGC CAG GCC ATG 240  
241 TCA GTC ATC CAT AAC TTA CAG AGA GAC AGC ACC CAA CGC TTA GAC CTG GAG GCC ACC 300  
301 AAA GCT CGA CTC AGC TCC CTG GAG AGC CTC CTC CAC CAA TTG ACC TTG GAC CAG CAG GCT GCC 360  
361 AGG CCC CAG GAG ACC CAG GAG GGG CTG CAG AGG GAG CTG GGC ACC CTG AGG CGG GAG CGG 420  
421 GAC CAG CTG GAA ACC CAA ACC AGA GAG TTG GAG ACT GCC TAC AGC AAC CTC CTC CGA GAC 480  
481 AAG TCA GTT CTG GAG GAA GAG AAG CGA CTA AGG CAA GAA AAT GAG AAT CTG GCC AGG 540  
541 AGG TTG GAA AGC AGC CAG GAG GTA GCA AGG CTG AGA AGG GGC CAG TGT CCC CAG ACC 600  
601 CGA GAC ACT GCT CGG GCT GTG CCA CCA GGC TCC AGA GAA GTT TCT ACG TGG AAT TTG GAC 660  
661 ACT TTG GCC TTC CAG GAA CTG AAG TCC GAG CTA ACT GAA GTT CCT GCT TCC CGA ATT TTG 720  
721 AAG GAG AGC CCA TCT GGC TAT CTC AGG AGT GGA GAG GGA GAC ACC GGA TGT GGA GAA CTA 780  
781 GTT TGG GTA GGA GAG CCT CTC ACG CTG AGA ACA GCA GAA ACA ATT ACT GGC AAG TAT GGT 840  
841 GTG TGG ATG CGA GAC CCC AAG CCC ACC TAC CCC TAC ACC CAG GAG ACC ACG TGG AGA ATC 900

FIG.7A

901 GAC ACA GTT GGC ACG GAT GTC CGC CAG GTT TTT GAG TAT GAC CTC ATC AGC CAG TTT ATG 960  
961 CAG GGC TAC CCT TCT AAG GTT CAC ATA CTG CCT AGG CCA CTG GAA AGC ACG GGT GCT GTG 1020  
1021 GTG TAC TCG GGG AGC CTC TAT TTC CAG GGC GCT GAG TCC AGA ACT GTC ATA AGA TAT GAG 1080  
1081 CTG AAT ACC GAG ACA GTG AAG GCT GAG AAG GAA ATC CCT GGA GCT GCC TAC CAC GGA CAG 1140  
1141 TTC CCG TAT TCT TGG GGT GGC TAC ACG GAC ATT GAC TTG GCT GTG GAT GAA GCA GGC CTC 1200  
1201 TGG GTC ATT TAC AGC ACC GAT GAG GCC AAA GGT GCC ATT GTC CTC TCC AAA CTG AAC CCA 1260  
1261 GAG AAT CTG GAA CTC GAA CAA ACC TGG GAG ACA AAC ATC CGT AAG CAG TCA GTC GCC AAT 1320  
1321 GCC TTC ATC ATC TGT GGC ACC TTG TAC ACC GTC AGC AGC TAC ACC TCA GCA GAT GCT ACC 1380  
1381 GTC AAC TTT GCT TAT GAC ACA GGC ACA GGT ATC AGC AAG ACC CTG ACC ATC CCA TTC AAG 1440  
1441 AAC CGC TAT AAG TAC AGC ATG ATT GAC TAC AAC CCC CTG GAG AAG CTC TTT GCC 1500  
1501 TGG GAC AAC TTG AAC ATG GTC ACT TAT GAC ATC AAG CTC TCC AAG ATG 1548

FIG.7B

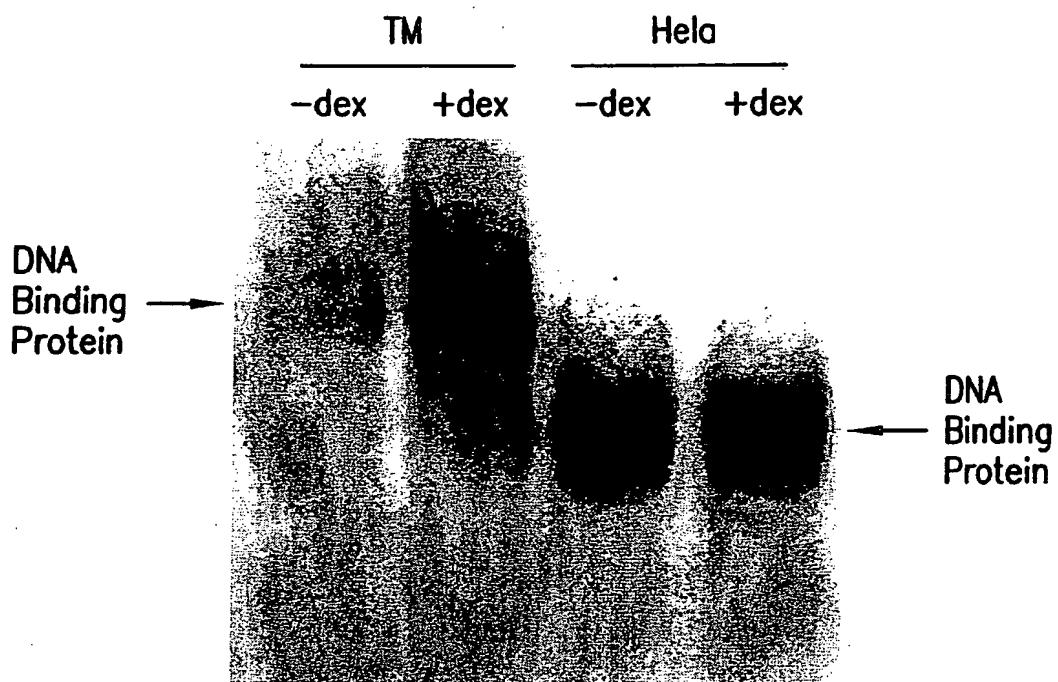
1 Met Arg Phe Phe Cys Ala Arg Cys 20  
21 Cys Ser Phe Gly Pro Glu Met Pro Ala Val Gln Leu Leu Leu Ala Cys Leu Val Trp 40  
41 Asp Val Gly Ala Arg Thr Ala Gln Leu Arg Lys Ala Asn Asp Gln Ser Gly Arg Cys Gln 60  
61 Tyr Thr Phe Ser Val Ala Ser Pro Asn Glu Ser Ser Cys Pro Glu Gln Ser Gln Ala Met 80  
81 Ser Val Ile His Asn Leu Gln Arg Asp Ser Ser Thr Gln Arg Leu Asp Leu Glu Ala Thr 100  
101 Lys Ala Arg Leu Ser Ser Leu Glu Ser Leu His Gln Leu Thr Leu Asp Gln Ala Ala 120  
121 Arg Pro Gln Glu Thr Gln Glu Gly Leu Gln Arg Glu Leu Gly Thr Leu Arg Arg Glu Arg 140  
141 Asp Gln Leu Glu Thr Gln Thr Arg Glu Leu Glu Thr Ala Tyr Ser Asn Leu Leu Arg Asp 160  
161 Lys Ser Val Leu Glu Glu Glu Lys Lys Arg Leu Arg Gln Glu Asn Glu Asn Leu Ala Arg 180  
181 Arg Leu Glu Ser Ser Gln Glu Val Ala Arg Leu Arg Arg Gly Gln Cys Pro gln Thr 200  
201 Arg Asp Thr Ala Arg Ala Val Pro Pro Gly Ser Arg Glu Val Ser Thr Trp Asn Leu Asp 220  
221 Thr Leu Ala Phe Gln Glu Ieu Lys Ser Glu Leu Thr Glu Val Pro Ala Ser Arg Ile Leu 240  
241 Lys Glu Ser Pro Ser Gly Tyr Leu Arg Ser Gly Glu Gly Asp Thr Gly Cys Gly Glu Leu 260  
261 Val Trp Val Gly Glu Pro Leu Thr Leu Arg Thr Ala Glu Thr Ile Thr Gly Lys Tyr Gly 280  
281 Val Trp Met Arg Asp Pro Lys Pro Thr Tyr Pro Tyr Thr Gln Glu Thr Trp Arg Ile 300

FIG.8A

301 Asp Thr Val Gly Thr Asp Val Arg Gln Val Phe Glu Tyr Asp Leu Ile Ser Gln Phe Met 320  
321 Gln Gly Tyr Pro Ser Lys Val His Ile Leu Pro Arg Pro Leu Glu Ser Thr Gly Ala Val 340  
341 Val Tyr Ser Gly Ser Leu Tyr Phe Gln Gly Ala Glu Ser Arg Thr Val Ile Arg Tyr Glu 360  
361 Leu Asn Thr Glu Thr Val Lys Ala Glu Lys Glu Ile Pro Gly Ala Gly Tyr His Gly Gln 380  
381 Phe Pro Tyr Ser Trp Gly Gly Tyr Thr Asp Ile Asp Leu Ala Val Asp Glu Ala Gly Leu 400  
401 Trp Val Ile Tyr Ser Thr Asp Glu Ala Lys Gly Ala Ile Val Leu Ser Lys Leu Asn Pro 420  
421 Glu Asn Leu Glu Leu Gln Thr Trp Glu Thr Asn Ile Arg Lys Gln Ser Val Ala Asn 440  
441 Ala Phe Ile Ile Cys Gly Thr Leu Tyr Thr Val Ser Ser Tyr Thr Ser Ala Asp Ala Thr 460  
461 Val Asn Phe Ala Tyr Asp Thr Gly Ile Ser Lys Thr Leu Thr Ile Pro Phe Lys 480  
481 Asn Arg Tyr Lys Tyr Ser Ser Met Ile Asp Tyr Asn Pro Leu Glu Lys Lys Leu Phe Ala 500  
501 Trp Asp Asn Leu Asn Met Val Thr Tyr Asp Ile Lys Leu Ser Lys Met

FIG.8B

### Gel Shift Assays



**FIG.9A**

**SUBSTITUTE SHEET (RULE 26)**

### Gel Shift Assays

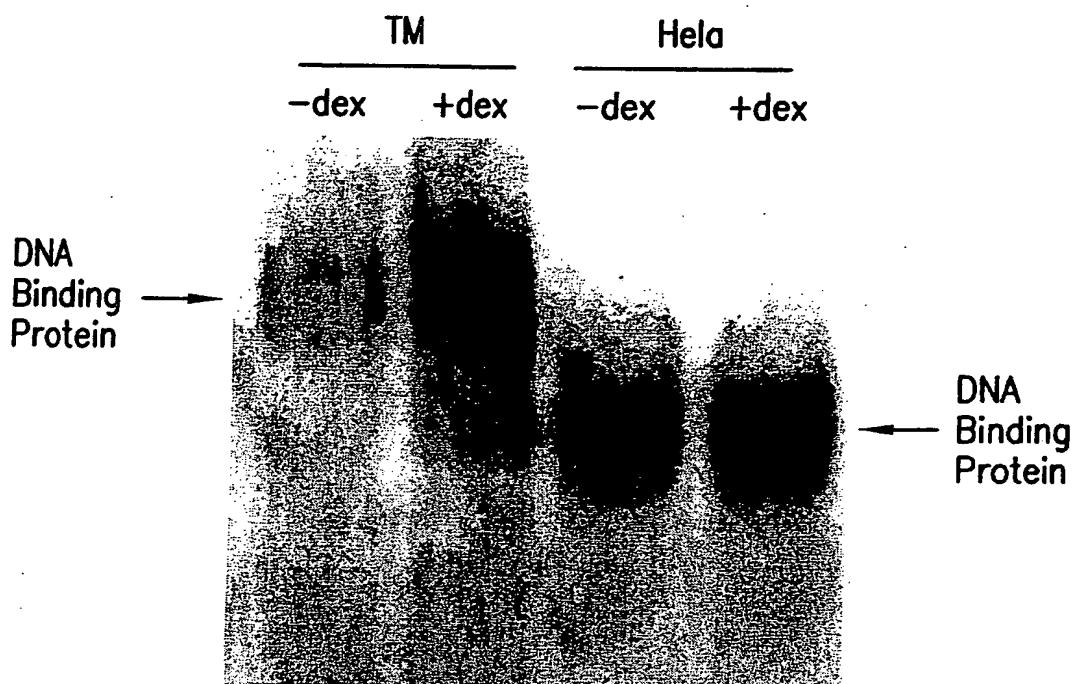


FIG. 9B

SUBSTITUTE SHEET (RULE 26)

## SEQUENCE LISTING

## (1) GENERAL INFORMATION

(i) APPLICANT: Nguyen, Thai D.  
Polansky, Jon R.  
Chen, Pu  
Chen, Hua

(ii) TITLE OF THE INVENTION: NUCLEIC ACIDS, KITS, AND METHODS FOR THE  
DIAGNOSIS, PROGNOSIS AND TREATMENT OF GLAUCOMA AND RELATED DISORDERS

(iii) NUMBER OF SEQUENCES: 38

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Howrey & Simon  
(B) STREET: 1299 Pennsylvania Avenue, N.W.  
(C) CITY: Washington  
(D) STATE: DC  
(E) COUNTRY: USA  
(F) ZIP: 20004-2402

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Diskette  
(B) COMPUTER: IBM Compatible  
(C) OPERATING SYSTEM: DOS  
(D) SOFTWARE: FastSEQ for Windows Version 2.0

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:  
(B) FILING DATE:  
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: 09/227,881  
(B) FILING DATE: 11-JAN-1999

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME:  
(B) REGISTRATION NUMBER:  
(C) REFERENCE/DOCKET NUMBER: 07425-0051

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 202 783-0800  
(B) TELEFAX: 202 383-6610  
(C) TELEX:

## (2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5300 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

ATCTTTGTTC AGTTTACCTC AGGGCTATTA TGAAATGAAA TGAGATAACC AATGTGAAAG  
TCCTATAAAC TGTATAGCCT CCATTCGGAT GTATGTCTT GGCAGGATGA TAAAGAATCA

60  
120

GGAAGAAGGA	GTATCCACGT	TAGCCAAGTG	TCCAGGCTGT	GTCTGCTCTT	ATTTTAGTGA	180
CAGATGTTGC	TCCTGACAGA	AGCTATTCTT	CAGGAAACAT	CACATCCAAT	ATGGTAAATC	240
CATCAAACAG	GAGCTAAGAA	ACAGGAATGA	GATGGGCACT	TGCCCAAGGA	AAAATGCCAG	300
GAGGAAAT	AATGATGAAA	AATAAACCTT	TCCCTTGT	TTAATTCA	GGAAAAAATG	360
ATGAGGACCA	AAATCAATGA	ATAAGGAAAA	CAGCTCAGAA	AAAAGATGTT	TCCAATTGG	420
TAATTAAGTA	TTTGTTCCTT	GGGAAGAGAC	CTCCATGTGA	GCTTGATGGG	AAAATGGAA	480
AAACGTCAA	AGCATGATCT	GATCAGATCC	CAAAGTGGAT	TATTATTTA	AAAACAGAT	540
GGCATCACTC	TGGGGAGGCA	AGTTCAGGAA	GTCATGTTA	GCAAAGGACA	TAACAATAAC	600
AGCAAATCA	AAATTCCGCA	AATGCAGGAG	GAAATGGGG	ACTGGGAAAG	CTTCATAAC	660
AGTGATTAGG	CAGTTGACCA	TGTTGCAAC	ACCTCCCCGT	CTATACCAGG	GAACACAAAA	720
ATTGACTGGG	CTAAGCCTGG	ACTTTCAAGG	GAAATATGAA	AAACTGAGAG	AAAAACAAAA	780
GACATGGTTA	AAAGGCAACC	AGAACATTGT	GAGCCTTCAA	AGCAGCAGTG	CCCCTCAGCA	840
GGGACCCCTGA	GGCATTTGCC	TTTAGGAAGG	CCAGTTTCT	TAAGGAATCT	TAAGAAACTC	900
TTGAAAGATC	ATGAATTTTA	ACCATTAA	GTATAAAAACA	AATATGCGAT	GCATAATCAG	960
TTTAGACATG	GGTCCCAATT	TTATAAAAGTC	AGGCATACAA	GGATAACGTG	TCCCAGCTCC	1020
GGATAGGTCA	GAAATCATT	GAAATCACTG	TGTCCCCATC	CTAACTTTTT	CAGAATGATC	1080
TGTCATAGCC	CTCACACACA	GGCCCGATGT	GTCTGACCTA	CAACCACATC	TACAACCCAA	1140
GTGCCTCAAC	CATTGTTAAC	GTGTATCTC	AGTAGGTCCC	ATTACAAATG	CCACCTCCCC	1200
TGTGCAGCCC	ATCCCCTC	ACAGGAAGTC	TCCCCACTCT	AGACTTCTGC	ATCACGATGT	1260
TACAGCCAGA	AGCTCCGTGA	GGGTGAGGGT	CTGTGCTTA	CACCTACCTG	TATGCTCTAC	1320
ACCTGAGCTC	ACTGCAACCT	CTGCCCTCCA	GGTTCAAGCA	ATTCTCCTGT	CTCAGCCTCC	1380
CGCGTAGCTG	GGACTACAGG	CGCACCCCCG	GTAATTTT	GTATTGTTAG	TAGAGATGGG	1440
GTTCACCAT	ATTAGCCGG	CTGGTCTTGA	ACTCCTGACC	TCAGGTGATC	CACCCACCTC	1500
AGCCTCTAA	AGTGTGGGA	TTACAGGCAT	GAGTCACCGC	GCCCCGCCAA	GGGTCAGTGT	1560
TTAATAAGGA	ATAACTTGA	TGGTTTACTA	AACCAACAGG	GAAACAGACA	AAAGCTGTGA	1620
TAATTTCAGG	GATTCTGGG	ATGGGAATG	GTGCCATGAG	CTGCTGCCT	AGTCCCAGAC	1680
CACTGGTCT	CATCACTTT	TTCCCTCATC	CTCATTTC	GGCTAAGTTA	CCATTTTATT	1740
CACCATGCTT	TTGTGGTAAG	CCTCCACATC	GTACTGAAA	TAAGAGTATA	CATAAAACTAG	1800
TTCCATTG	GGCCATCTGT	GTGTGTGTAT	AGGGGAGGAG	GGCATACCC	AGAGACTCCT	1860
TGAAGCCCC	GGCAGAGGTT	TCCTCTCCAG	CTGGGGGAGC	CCTGCAAGCA	CCCGGGGTCC	1920
TGGGTGTCT	GAGCACCTG	CCAGCCCGTG	CCACTGGTTG	TTTGTATC	ACTCTCTAGG	1980
GACCTGTG	TTTCTATTTC	TGTGTACTC	GTTCATTCAT	CCAGGCATT	ATTGACAATT	2040
TATTGAGTAC	TTATATCTG	CAGACACCAG	AGACAAAATG	GTGAGCAAAG	CAGTCACTGC	2100
CCTACCTTC	TGGAGGTGAC	AGTTCTCAT	GGAAGACGTG	CAGAAGAAA	TTAATAGCCA	2160
GCCAACTAA	ACCCAGTGT	GAAAGAAAGG	AAATAAACAC	CATCTTGAAG	AATTGTGCGC	2220
AGCATCC	AAACAAGGCC	CCTCCCTAGC	GCCCCCTGCT	GCCTCCATCG	TGCCCCGGAGG	2280
CCCCCAAGCC	CGAGTCTTC	AAGCCTCC	CTCCATCAGT	CACAGCGCTG	CAGCTGGCCT	2340
GCCTCGCTTC	CCGTGAATCG	TCCTGGTGA	TCTGAGCTG	AGACTCCTTG	GCTCCAGGCT	2400
CCAGAAAGGA	AATGGAGAGG	GAAACTAGTC	TAACGGGAA	TCTGGAGGGG	ACAGTGTTC	2460
CTCAGAGGGA	AAGGGGCTC	CACGTTCCAGG	GAATTCCAG	GAGGTGGGGG	CTGCAGGGAG	2520
TGGGGACGCT	GGGGCTGAGC	GGGTGTGAA	AGGCAGGAAG	GTGAAAAGGG	CAAGGCTGAA	2580
GCTGCCAGA	TGTTCACTG	TGTTCACGGG	GCTGGGAGTT	TTCCGTTGCT	TCCTGTGAGC	2640
CTTTTTATCT	TTTCTCTGCT	TGGAGGAGAA	GAAGTCTATT	TCATGAAGGG	ATGCAGTTTC	2700
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TTAATGGGAA	TATAGGAAGC	GAGCTCATT	CCTAGGCCGT	TAATTCAACGG	AAGAAGTGCAC	2820
TGGAGTCTT	TCTTCATGT	CTTCTGGGCA	ACTACTCAGC	CCTGTGGTGG	ACTTGGCTTA	2880
TGCAAGACGG	TGAAAACCT	TGGAATCAGG	AGACTCGTT	TTCTTTCTGG	TTCTGCTT	2940
GGTTGGCTGT	GCGACCGTGG	GCAAGTGTCT	CTCCTCCCT	GGGCCATAGT	CTTCTCTGCT	3000
ATAAAAGACCC	TTGCAGCTCT	CGTGTCTGT	GAACACTTCC	CTGTGATTCT	CTGTGAGGGGG	3060
GGATGTTGAG	AGGGGAAGGA	GGCAGAGCTG	GAGCAGCTGA	GCCACAGGGG	AGGTGGAGGG	3120
GGACAGGAAG	GCAGGCAGAA	GCTGGGTG	CCATCAGTCC	TCACTGATCA	CGTCAGACTC	3180
CAGGACCGAG	AGCCACAAATG	CTTCAGGAAA	GCTCAATGAA	CCCAACAGCC	ACATTTCCT	3240
TCCCCTAAGCA	TAGACAATGG	CATTGCAA	TAACCAAAA	GAATGCAGAG	ACTAACTGGT	3300
GGTAGCTTT	GCCTGGCATT	CAAAAACCTGG	GCCAGAGCA	GTGGAAAATG	CCAGAGATTG	3360
TTAAACTTT	CACCCCTGACC	AGCACCCAC	GCAGCTCAGC	AGTGAATGCT	GACAGCACGG	3420
AGTGACCTGC	AGCGCAGGGG	AGGAGAAGAA	AAAGAGAGGG	ATAGTGTATG	AGCAAGAAAAG	3480
ACAGATTCA	TCAAGGGCAG	TGGGAATTGA	CCACAGGGAT	TATAGTCCAC	GTGATCCTGG	3540
GTTCTAGGAG	GCAGGGCTAT	ATTGTGGGGG	GAAAAAAATCA	GTTCAGGGGA	AGTCGGGAGA	3600
CCTGATTCT	AATACTATAT	TTTCCCTTTA	CAAGCTGAGT	AATTCTGAGC	AAGTCACAAG	3660
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GGAGTTAGCA	GCACAAGGGC	AATCCGTTT	CTTTTAACAG	GAAGAAAACA	TTCCCTAAGAG	3780
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CATTCAGCG	ATGTTACTA	TCTGATTCA	AAAATGAGAC	TAGTACCTCT	TGGTCAGCTG	3900
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AAGAATAGAA	TCTTTAGAGC	AAACTGTGTT	TCTCCACTCT	GGAGGTGAGT	CTGCCAGGGC	4020
AGTTTGAAA	TATTTACTTC	ACAAGTATTG	ACACTGTTGT	TGGTATTAAC	AACATAAAAGT	4080
TGCTCAAAGG	CAATCATTAT	TTCAAGTGGC	TTAAAGTTAC	TTCTGACAGT	TTTGGTATAT	4140

TTATTGGCTA TTGCCATTTG CTTTTGTTT TTTCTCTTG GGTTTATTAA TGTAAAGCAG	4200
GGATTATTAAC CCTACAGTCC AGAAAGCCTG TGAATTGAA TGAGGAAAAA ATTACATTTT	4260
TGTTTTTACCC ACCTTCAAC TAAATTAAAC ATTTTATTCC ATTGCGAATA GAGCCATAAA	4320
CTCAAAGTGG TAATAACAGT ACCTGTGATT TTGTCATTAC CAATAGAAAT CACAGACATT	4380
TTATACTATA TTACAGTTGT TGAGATAACG TTGTAAGTGA AATATTATA CTAAAACATA	4440
CTTTGAAATT AGACCTCTG CTGGATCTTG TTTTAACAT ATTAATAAAA CATGTTAAA	4500
ATTTTGATAT TTGATAATC ATATTTCATT ATCATTTGTT TCCTTGTAA TCTATATTTT	4560
ATATATTGA AAACATCTT CTGAGAAGAG TTCCCCAGAT TTCACCAATG AGGTTCTTGG	4620
CATGCACACA CACAGAGTAA GAACTGATT AGAGGCTAAC ATTGACATTG GTGCCTGAGA	4680
TGCAAGACTG AAAATTAGAAA GTTCTCCCAA AGATAACACAG TTGTTTAAA GCTAGGGGTG	4740
AGGGGGAAA TCTGCCGTT CTATAGGAAT GCTCTCCCTG GAGCCTGGTA GGGTGCCTGTC	4800
CTTGTGTTCT GGCTGGCTGT TATTTTCTC TGTCCTGCT ACCTTAAAGG GGACTTGT	4860
GGATCTCCAG TTCTAGCAT AGTGCTGAGC ACAGTGCAGG TTCTCAATGA GTTTGCAGAG	4920
TGAATGGAAA TATAAACTAG AAATATATCC TTGTTGAAAT CAGCACACCA GTAGTCCTGG	4980
TGTAAGTGTG TGTACGTGTG TGTTGTGTG TGTTAAACCA GGTGGAGATA	5040
TAGGAACATAT TATTGGGTA TGTTGCATA AATTGGGATG TTCTTTTAA AAAGAAACTC	5100
CAAACAGACT TCTGGAAGGT TATTTCTAA GAATCTGCT GGCAGCGTGA AGGCAACCCC	5160
CCTGTGACA GCCCCACCA GCCTCACGTG GCCACCTCTG TCTCCCCCA TGAAGGGCTG	5220
GCTCCCCAGT ATATATAAAC CTCTCTGGAG CTCGGGCATG AGCCAGCAAG GCCACCCATC	5280
CAGGCACCTC TCAGCACACAGC	5300

## (2) INFORMATION FOR SEQ ID NO:2:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5304 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

ATCTTTGTTG AGTTTACCTC AGGGCTATTAA TGAAATGAAA TGAGATAACC AATGTGAAAG	60
TCCTTATAAAC TGATAGCCT CCATTGCGAT GTATGCTTT GGCAGGATGA TAAAGAATCA	120
GGAAAGAAGGA GTATCCACGT TAGCCAAGTG TCCAGGCTGT GTCTGCTCTT ATTTTAGTGA	180
CAGATGTTGC TCTGTGACAGA AGCTATTCTT CAGGAAACAT CACATCCAAT ATGGTAAATC	240
CATCAAACAG GAGCTAAGAA ACAGGAATGA GATGGGCACT TGCCCAAGGA AAAATGCCAG	300
GAGAGCAAAT AATGATGAAA AATAAACTTT TCCCTTTGTT TTTAATTCA CGAAAAAAATG	360
ATGAGGACCA AAATCAATGA ATAAGGAAAA CAGCTCAGAA AAAAGATGTT TCCAAATTGG	420
TAATTAAGTA TTTGTTCCCTT GGGGAAGAGAC CTCCATGTGA GCTGTGAGG AAAATGGGAA	480
AAACGTCAAA AGCATGATCT GATCAGATCC CAAAGTGGAT TATTATTTA AAAACCAGAT	540
GGCATCACTC TGGGGAGGCA AGTTTCAAGG GGTCTGTTA GCAAAGGACA TAACAATAAC	600
AGCAAAATCA AAATTCCGCA AATGCAAGG GAAATATGAA AAACAGAG GAAACACAAA	660
AGTGATTAGG CAGTTGACCA TGTTGCAAC ACCTCCCCGT CTATACCAGG GAACACACAA	720
ATTGACTGGG CTAAGCCTGG ACTTTCAAGG GAGCCTCAA AGCAGCAGTG CCCCTCAGCA	780
GACATGGTTA AAAGGCAACC AGAACATTGT GGCATTTGCC TTAAGGAATCT TAAGAAACTC	840
GGGACCCCTGA GGCATTTGCC TTTAGGAAGG GTATAAAACA AATATGCGAT GCATAATCAG	900
TTGAAAGATC ATGAATTAA ACCATTTAA AGGCATACAA GGATAACGTG TCCCAGCTCC	960
TTTAGACATG GGTCCCAATT TTATAAAGTC TGTCCCCATC CTAACCTTTT CAGAATGATC	1020
GGATAGGTCA GAAATCATTA GAAATCACTG GTCTGACCTA CAAACACATC TACAACCAA	1080
TGTCTAGGCC CTCACACACA GGCCCGATGT AGTAGGTCCC ATTACAAATG CCACCTCCCC	1140
GTGCTCAAC CATTGTTAAC GTGTCATCTC TCCCCACTCT AGACTTCTGC ATCACGATGT	1200
TGTGCAAGCC ATCCCGCTCC ACAGGAAGTC CTGTGTCTTA CACCTACCTG TATGCTCTAC	1260
TACAGCCAGA AGCTCCGTGA GGGTGAGGGT GGTTCAAGCA ATTCTCCTGT CTCAGCCTCC	1320
ACCTGAGCTC ACTGCAACCT CTGCCCTCCCA GCTAATTGTT GTATTGTTAG TAGAGATGGG	1380
CGCGTAGCTG GGACTACAGG CGCACGCCCG ACTCCTGACC TCAGGTGATC CACCCACCTC	1440
GTTTCACCAT ATTAGCCCCG CTGGTCTTGA GAGTCACCGC GCCCGGCCAA GGGTCAGTGT	1500
AGCCTCCTAA AGTGTGGGA TTACAGGCAT CTGCTGCTGAG AGACCAACAGG GAAACAGACA AAAGCTGTGA	1560
TTAATAAGGA ATAACATTGAA TGGTTTACTA GTGCCATGAG CTGCCCTGCC AGTCCCAGAC	1620
TAATTTCAGG GATTCTTGGG ATGGGGAAATG CTCATTTCG GGCTAAGTTA CCATTTATT	1680
CACTGGCTCT CATCACTTTC TTCCCTCATC GTTACTGAAA TAAGAGTATA CATAAACTAG	1740
CACCATGCTT TTGTGGTAAG CCTCCACATC AGGGGAGGAG GGCATACCCC AGAGACTCCT	1800
TTCCATTGTC GGCCATCTGT GTGTGTGTAG CTGGGGGAGC CCTGCAAGCA CCCGGGGTCC	1860
TGAAGCCCCC GGCAGAGGGT TCCTCTCCAG CCACTGTTG TTTTGTATC ACTCTCTAGG	1920
TGGGTGTCCT GAGCAACCTG CCAGCCCCGTG GTTCATTCAT CCAGGCATTC ATTGACAATT	1980
GACCTGTTGC TTTCTATTTT TGTTGACTC AGACAAAATG GTGAGCAAAG CAGTCACTGC	2040
TATTGAGTAC TTATATCTGC CAGACACCAG	2100

CCTACCTTCG	TGGAGGTGAC	AGTTTCTCAT	GGAAGACGTG	CAGAAGAAAA	TTAATAGCCA	2160
GCCAACTTAA	ACCCAGTGCT	GAAAGAAAAG	AAATAAACAC	CATCTGAAG	AATTGTGCCG	2220
AGCATCCCTT	AAACAAGGCCA	CCTCCCTAGC	GCCCCCTGCT	GCCTCCATCG	TGCCCAGGAGG	2280
CCCCCAAGCC	CGAGTCTTCC	AAGCCTCCTC	CTCCATCAGT	CACAGCGCTG	CAGCTGGCCT	2340
GCCTCGCTTC	CCGTGAATCG	TCCTGGTGCA	TCTGAGCTGG	AGACTCCTTG	GCTCCAGGCT	2400
CCAGAAAGGA	AATGGAGAGG	GAAACTAGTC	TAACGGAGAA	TCTGGAGGGG	ACAGTGTTC	2460
CTCAGAGGGA	AAGGGGCCTC	CACGTCCAGG	AGAATTCCAG	GAGGTGGGGA	CTGCAGGGAG	2520
TGGGGACGCT	GGGGCTGAGC	GGGTGCTGAA	AGGCAGGAAG	GTGAAAAGGG	CAAGGCTGAA	2580
GCTGCCAGA	TGTTCACTGT	TGTTCACGGG	GCTGGGAGTT	TTCCGGTGT	TCCTGTGAGC	2640
CTTTTATCT	TTTCTCTGT	TGGAGGAGAA	GAAGTCTATT	TCATGAAGGG	ATGCAGTTTC	2700
ATAAAAGTCAG	CTGTTAAAAT	TCCAGGGTGT	GCATGGGTT	TCCTTCACGA	AGGCCTTAT	2760
TTAATGGGAA	TATAGGAAGC	GAGCTCATTT	CCTAGGCCGT	TAATTACACGG	AAGAAGTGAC	2820
TGGAGTCTT	TCTTTCATGT	CTTCTGGCA	ACTACTCAGC	CCTGTGGTGG	ACTTGGCTTA	2880
TGCAAGACGG	TCGAAAACCT	TGGAATCAGG	AGACTCGGTT	TTCTTTCTGG	TTCTGCCATT	2940
GGTTGGCTGT	GCGACCGTGG	GCAAGTGTCT	CTCCTTCCCT	GGGCCATAGT	CTTCTCTGCT	3000
ATAAAAGACCC	TTGAGCTCT	CGTGTCTGT	GAACACTTCC	CTGTGATTCT	CTGTGAGGGG	3060
GGATGTTGAG	AGGGGAAGGA	GGCAGAGCTG	GAGCAGCTGA	GCCACAGGGG	AGGTGGAGGG	3120
GGACAGGAAG	GCAGGCAGAA	GCTGGGTGT	CCATCAGTCC	TCACTGATCA	CGTCAGACTC	3180
CAGGACCGAG	AGCCACAAATG	CTTCAGGAAA	GCTCAATGAA	CCCAACAGCC	ACATTTCCCT	3240
TCCCTAACAGA	TAGACAATGG	CATTGCCAA	TAACCAAAAA	GAATGCAGAG	ACTAACTGGT	3300
GGTAGCTTTT	GCCTGGCATT	CAAAAACCTGG	GCCAGAGCAA	GTGAAAATG	CCAGAGATTG	3360
TTAAACTTTT	CACCTGACC	AGCACCCCCAC	GCAGCTCAGC	AGTACTGCT	GACAGCACGG	3420
AGTACCTGC	AGGGCAGGGG	AGGAGAAGAA	AAAGAGAGGG	ATAGTGTATG	AGCAAGAAAG	3480
ACAGATTCA	TCAAGGGCAG	TGGGAATTGA	CCACAGGGAT	TATAGTCCAC	GTGATCCTGG	3540
GTTCTAGGAG	GCAGGGCTAT	ATTGTTGGGG	AAAAAAATCA	GTTCAAGGGGA	AGTCGGGAGA	3600
CCTGATTCT	AATACTATAT	TTTCTTTA	CAAGCTGAGT	AATTCTGAGC	AAGTCACAAG	3660
GTAGTAAC	AGGCTGTAAG	ATTACTAGT	TTCTCCTTAT	TAGGAACCTCT	TTTTCTCTGT	3720
GGAGTTAGCA	GCACAAGGGC	AATCCGTTT	CTTTTAACAG	GAAGAAAACA	TTCTTAAGAG	3780
TAAAGCCAAA	CAGATTCAAG	CCTAGGTCTT	GCTGACTATA	TGATTGGTT	TTTGAAGAAAT	3840
CATTCAGCG	ATGTTTACTA	TCTGATTCAAG	AAAATGAGAC	TAGTACCCCTT	TTGTCAGCTG	3900
TAAACAAACA	CCCATTGTAA	AATGCTCTAA	GTTCAGGCTT	AACTGCAGAA	CCAATCAAAT	3960
AAGAATAGAA	TCTTTAGAGC	AAACTGTGTT	TCTCCACTCT	GGAGGTGAGT	CTGCCAGGGC	4020
AGTTTGGAAA	TATTTACTTC	ACAAGTATTG	ACACTGTGTT	TGGTATTAAAC	AACATAAAAGT	4080
TGCTCAAAGG	CAATCATTAT	TTCAAGTGGC	TTAAAGTTAC	TTCTGACAGT	TTTGGTATAT	4140
TTATTGGCTA	TTGCCATTG	CTTTTGTGTT	TTTCTCTTTG	GGTTTATTAA	TGAAAGCAG	4200
GGATTATTAA	CCTACAGTCC	AGAAAAGCTG	TGAATTGAA	TGAGGAAAAAA	ATTACGTTTT	4260
TATTTTAC	ACCTCTAAC	TAAATTAAAC	ATTTTATTC	ATTGCGAATA	GAGCCATAAA	4320
CTCAAAGTGG	TAATAGAGT	ACCTGTGATT	TTGTCATTAC	CAATAGAAAT	CACAGACATT	4380
TTTACATATA	TTACAGTTGT	TGCAGGTACG	TTGTAAGTGA	AAATATTATA	CTCAAAACTA	4440
CTTGAATT	AGACCTCCCTG	CTGGATCTTG	TTTTTAACAT	ATTAATAAAA	CATGTTAAA	4500
ATTTTGATAT	TTTGATAATC	ATATTTCATT	ATCATTTGT	TCCTTTGTAA	TCTATATTTT	4560
ATATATTGTA	AAACATCTT	CTGAGAAGAG	TTCCCCAGAT	TTCAACATG	AGGTTCTTGG	4620
CATGCACACA	CACAGAGTAA	GAACGTGATT	AGAGGCTAAC	ATTGACATTG	GTGCCTGAGA	4680
TGCAAGACTG	AAATTAGAAA	GTTCTCCCAA	AGATACACAG	TTGTTTTAAA	GCTAGGGGTG	4740
AGGGGGAAA	TCTGCCGCTT	CTATAGGAAT	GCTCTCCCTG	GAGCCTGGTA	GGGTGCTGTC	4800
CTTGTGTTCT	GGCTGGCTG	TATTTTCTC	TGTCCTCGCT	ACGTCTTAAA	GGACTGTGTT	4860
GGATCTCCAG	TTCTAGCAT	AGTGCCTGGC	ACAGTGCAGG	TTCTCAATGA	GTTCAGAG	4920
TGAATGGAAA	TATAAACTAG	AAATATATCT	TTGTTGAAT	CAGCACACCA	GTAGTCTGG	4980
TGTAAGTGTG	TGTACGTGTG	TGTGTGTGTG	TGTGTGTG	TGTGTGTAAA	ACCAGGTGGA	5040
GATATAGGAA	CTATTATTGG	GGTATGGGTG	CATAAATTGG	GATGTTCTTT	TTAAAAAGAA	5100
ACTCCAAACA	GACTTCTGGA	AGGTTATT	CTAAGAAATCT	TGCTGGCAGC	GTGAAGGCAA	5160
CCCCCTGTG	CACAGCCCCA	CCCAGCCTCA	CGTGGCCACC	TCTGTCTTCC	CCCATGAAGG	5220
GCTGGCTCCC	CAGTATATAT	AAACCTCTCT	GGAGCTCGGG	CATGAGCCAG	CAAGGCCACC	5280
CATCCAGGCA	CCTCTCAGCA	CAGC				5304

## (2) INFORMATION FOR SEQ ID NO:3:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 6169 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ATCTTTGTTC AGTTTACCTC AGGGCTATTA TGAAATGAAA TGAGATAACC AATGTGAAAG

TCCTATAAAC	TGTATAGCCT	CCATTGGAT	GTATGCTTT	GGCAGGATGA	TAAAGAATCA	120
GGAAGAAGGA	GTATCCACGT	TAGCCAAGTG	TCCAGGCTGT	GTCTGCTCTT	ATTTTAGTGA	180
CAGATGTTGC	TCCTGACAGA	AGCTATTCTT	CAGGAAACAT	CACATCCAAT	ATGGTAAATC	240
CATCAAACAG	GAGCTAAGAA	ACAGGAATGA	GATGGGCACT	TGCCCAAGGA	AAAATGCCAG	300
GAGAGCAAAT	AATGATGAAA	AATAAACTTT	TCCCTTTGTT	TTAATTCA	GGAAAAAATG	360
ATGAGGACCA	AAATCAATGA	ATAAGGAAA	CAGCTCAGAA	AAAAGATGTT	TCCAAATTGG	420
TAATTAAGTA	TTTGTTCCTT	GGGAAGAGAC	CTCCATGTGA	GCTTGATGGG	AAAATGGGAA	480
AAACGTCAAA	AGCATGATCT	GATCAGATCC	CAAAGTGGAT	TATTATTTA	AAAACCAGAT	540
GGCATCACTC	TGGGGAGGCA	AGTTCAGGAA	GGTCATGTAA	GCAAAGGACA	TAACAATAAC	600
AGCAAAATCA	AAATTCCCGA	AATGCAAGG	GAAAATGGGG	ACTGGGAAAG	CTTCATAAC	660
AGTGTAGTAGG	CAGTTGACCA	TGTTGCAAC	ACCTCCCCGT	CTATACCAGG	GAACACAAAA	720
ATTGACTGGG	CTAAGCCTGG	ACTTCAAGG	GAAATATGAA	AAACTGAGAG	CAAACACAAA	780
GACATGGTTA	AAAGGCAACC	AGAACATTGT	GAGCCTTCAA	AGCAGCAGTG	CCCCTCAGCA	840
GGGACCTGAA	GGCATTGCCC	TTTAGGAAGG	CCAGTTTTCT	TAAGGAATCT	TAAGAAACTC	900
TTGAAAGATC	ATGAATTAA	ACCATTAA	GTATAAAACA	AATATGGAT	GCATAATCAG	960
TTTAGACATG	GGTCCCAATT	TTATAAAGTC	AGGCATACAA	GGTAAACGTG	TCCCAGCTCC	1020
GGATAGGTCA	GAAATCATTA	GAAATCACTG	TGTCCCCATC	CTAACTTTTT	CAGAATGATC	1080
TGTCTAGGCC	CTCACACACA	GGCCGATGT	GTCTGACCTA	CAACACATC	TACAACCAA	1140
GTGCTCAAC	CATTGTTAAC	GTGTCATCTC	AGTAGGTCCC	ATTACAAATG	CCACCTCCCC	1200
TGTGCAGCC	ATCCCGCTCC	ACAGGAAGTC	TCCCCACTCT	AGACTTCTGC	ATCACGATGT	1260
TACAGCCAGA	AGCTCCGTGA	GGGTGAGGGT	CTGTGCTTA	CACCTACCTG	TATGCTCTAC	1320
ACCTGAGCTC	ACTGCAACT	CTGCCCTCCA	GGTTCAAGCA	ATTCTCCTGT	CTCAGCCTCC	1380
CGCGTAGCTG	GGACTACAGG	CGCACGCCCG	GCTAATTTTT	GTATTGTTAG	TAGAGATGGG	1440
GTTTCACCAT	ATTAGCCCGG	CTGGTCTTGA	ACTCCTGACC	TCAGGTGATC	CACCCACCTC	1500
AGCCTCTAA	AGTGTGGGA	TTACAGGCAT	GAGTCACCGC	GCCCCGCCAA	GGGTCAGTGT	1560
TTAATAAGGA	ATAACTTGAA	TGGTTTACTA	AACCAACAGG	GAAACAGACA	AAAGCTGTGA	1620
TAATTTCAGG	GATTCTGGG	ATGGGAATG	GTGCGATGAG	CTGCTGCCT	AGTCCCAGAC	1680
CACTGGCCT	CATCACTTTC	TTCCCTCATC	CTCATTTCAT	GGCTAAGTTA	CCATTTTATT	1740
CACCATGCTT	TTGTGGTAAG	CCTCCACATC	GTTACTGAAA	TAAGAGTATA	CATAAACTAG	1800
TTCCATTGCG	GGCCATCTGT	GTGTGTGTAT	AGGGGAGGAG	GGCATAACCCC	AGAGACTCCT	1860
TGAAGCCCCC	GGCAGAGGTT	TCCTCTCCAG	CTGGGGGAGC	CCTGCAAGCA	CCC GG GTCC	1920
TGGGTGTCCCT	GAGCAACCTG	CCAGCCCGTG	CCACTGTTG	TTTTGTTATC	ACTCTCTAGG	1980
GACCTGTTGC	TTTCTATTTC	TGTGTGACTC	GTCATTCTAT	CCAGGCATTC	ATTGACAATT	2040
TATTGAGTAC	TTATATCTGC	CAGACACCAG	AGACAAAATG	GTGAGCAAAG	CAGTCACTGC	2100
CCTACCTTCG	TGGAGGTGAC	AGTTTCTCAT	GGAAAGACGTG	CAGAAGAAA	TTAATAGCCA	2160
GCCAACCTAA	ACCCAGTGT	GAAAGAAAGG	AAATAAACAC	CATCTGAAG	AATTGTGCGC	2220
AGCATCCCTT	AAACAAGGCCA	CCTCCCTAGC	GCCCCCTGCT	GCCTCCATCG	TGCCC GGAGG	2280
CCCCCCAAAGCC	CGAGCTTCTC	AAGCCTCTC	CTCCATCAGT	CACAGCGCTG	CAGCTGGCCT	2340
GCCTCGCTTC	CCGTGAATCG	TCCTGGTGCA	TCTGAGCTGG	AGACTCCCTG	GCTCCAGGGCT	2400
CCAGAAAGGA	AATGGAGAGG	GAAACTAGTC	TAACGGAGAA	TCTGGAGGGG	ACAGTGTTTTC	2460
CTCAGAGGGA	AAGGGGCCCTC	CACGTCCAGG	AGAATTCCAG	GAGGTGGGG	CTGCAGGGAG	2520
TGGGGACGCT	GGGGCTGAGC	GGGTGCTGAA	AGGCAGGAAG	GTGAAAAGGG	CAAGGCTGAA	2580
GCTGCCAGA	TGTTCACTGTT	TGTTCACGGG	GCTGGGAGTT	TTCCGTTGTC	TCCTGTGAGC	2640
CTTTTTATCT	TTTCTCTGCT	TGGAGGAGAA	GAAGTCTATT	TCATGAAGGG	ATGCAGTTTC	2700
ATAAAAGTCAG	CTGTTAAAT	TCCAGGGTGT	GCATGGGTTT	TCCTTCACGA	AGGCCTTTAT	2760
TTAATGGGAA	TATAGGAAGC	GAGCTCATT	CCTAGGCCGT	TAATTTCACGG	AAGAAGTGC	2820
TGGAGCTTTT	TCTTTCATGT	CTTCTGGGCA	ACTACTCAGC	CCTGTGGTGG	ACTTGGCTTA	2880
TGCAAGACGG	TCGAAACACT	TGGAATCAGG	AGACTCGGTT	TTCTTTCTGG	TTCTGCATT	2940
GGTTGGCTGT	GCGACCGTGG	GCAAGTGTCT	TCCTTCCTCCT	GGGCCATAGT	CTTCTCTGCT	3000
ATAAAAGACCC	TTGCAGCTCT	CGTGTTCCTGT	GAACACTTCC	CTGTGATTCT	CTGTGAGGGGG	3060
GGATGTTGAG	AGGGGAAGGA	GGCAGAGCTG	GAGCAGCTGA	GCCACAGGGG	AGGTGGAGGG	3120
GGACAGGAAG	GCAGGCAGAA	GCTGGGTGCT	CCATCAGTCC	TCACTGATCA	CGTCAAGACTC	3180
CAGGACCGAG	AGCCACAATG	CTTCAGGAAA	GCTCAATGAA	CCAAACAGGC	ACATTTCCT	3240
TCCCTAACCA	TAGACAATGG	CATTGCAA	TAACCAAAA	GAATGCAGAG	ACTAACTGGT	3300
GGTAGCTTTT	GCCTGGCATT	CAAAAACCTG	GCCAGAGCAA	GTGGAAAATG	CCAGAGATTG	3360
TTAAACTTTT	CACCCCTGACC	AGCACCCCC	GCAGCTCAGC	AGTGACTGCT	GACAGCACGG	3420
AGTGACCTGC	AGCAGCAGGGG	AGGAGAAGAA	AAAGAGAGGG	ATAGTGTATG	AGCAAGAAAG	3480
ACAGATTCTAT	TCAAGGGCAG	TGGGAATTGA	CCACAGGGAT	TATAGTCCAC	GTGATCTGTC	3540
GTTCTAGGAG	GCAGGGCTAT	ATTGTGGGGG	GAAAAAAATCA	GTTCAAGGGGA	AGTCGGGAGA	3600
CCTGATTCT	AATACTATAT	TTTTCCTTTA	CAAGCTGAGT	AATTCTGAGC	AAGTCACAAG	3660
GTAGTAAC TG	AGGCTGTAAG	ATTACTTAGT	TTCTCCTTAT	TAGGAACCTCT	TTTCTCTGT	3720
GGAGTTAGCA	GCACAAGGGC	AATCCCCTT	CTTTAACAG	GAAGAAAACA	TTCCAAGAG	3780
TAAAGCCAAA	CAGATTCAAG	CCTAGGTCTT	GCTGACTATA	TGATTGGTTT	TTGAAAAT	3840
CATTTCAGCG	ATGTTTACTA	TCTGATTCA	AAAATGAGAC	TAGTACCTCT	TGGTCAGCTG	3900
TAAACAAACA	CCCAGTTGTA	AATGTCTCAA	GTTCAAGGGCT	AACTGCAGAA	CCAATCAAAA	3960
AGAATAGAAT	CTTTAGAGCA	AACTGTGTTT	CTCCACATCT	GGAGGTGAGT	CTGCCAGGGC	4020
AGTTGGAAA	TATTTACTTC	ACAAGTATTG	ACACTGTGTT	TGGTATTAAC	AACATAAAAGT	4080

TGCTCAAAGG	CAATCATTAT	TTCAAGTGGC	TTAAAGTTAC	TTCTGACAGT	TTTGGTATAT	4140
TTATTGGCTA	TTGCCATTG	CTTTTGTTT	TTTCCTTGTG	GGTTTATTAA	TGTAAAGCAG	4200
GGATTATTAA	CCTACAGTCC	AGAAAGCCTG	TGAATTGAA	TGAGGAAAAA	ATTACATTTC	4260
TGTTTTAAC	ACCTTCTAAC	TAAATTAAAC	ATTTTATTCC	ATTGCGAATA	GAGCCATAAA	4320
CTCAAAGTGG	TAATAACAGT	ACCTGTGATT	TTGTCATTAC	CAATAGAAAT	CACAGACATT	4380
TTATRACTATA	TTACAGTTGT	TGCAGATACG	TTGTAAGTGA	AATATTATA	CTCAAAACTA	4440
CTTTGAAATT	AGACCTCTG	CTGGATCTTG	TTTTAACAT	ATTAATAAAA	CATGTTAAA	4500
ATTTTGATAT	TTTGATAATC	ATATTTCATT	ATCATTGTT	TCCTTGTAA	TCTATATTTC	4560
ATATATTGAA	AAACATCTT	CTGAGAAGAG	TTCCCAGAT	TTCACCAATG	AGGTTCTGG	4620
CATGCCACACA	CACAGAGTAA	GAACGTGATT	AGAGGCTAAC	ATTGACATTG	GTGCCCTGAGA	4680
TGCAAGACTG	AAATTAGAAA	GTTCTCCCAA	AGATACACAG	TTGTTTAAA	CCTAGGGGTG	4740
AGGGGGGAAA	TCTGCCGCTT	CTATAGGAAT	GCTCTCCCTG	GAGCCTGGTA	GGGTGCTGTC	4800
CTTGTGTCT	GGCTGGCTGT	TATTTTCTC	TGTCCTGCT	ACGTCTAAA	GGACTTGTTT	4860
GGATCTCCAG	TTCTTAGCAT	AGTGCCTGGC	ACAGTCAGG	TTCTCAATGA	GTTTGCAGAG	4920
TGAATGGAAA	TATAAACTAG	AAATATATCC	TGTTGAAT	CAGCACACCA	GTAGTCTGG	4980
TGTAAGTGTG	TGTACGTGTG	TGTGTGTGTG	TGTGTGTG	TGTAAAACCA	GGTGGAGATA	5040
TAGGAACAT	TATGGGGGT	TGGGTGCATA	AATTGGGATG	TTCTTTTAA	AAAGAAACTC	5100
CAAACAGACT	TCTGGAAGGT	TATTTCTAA	GAATCTGCT	GGCAGCGTGA	AGGCAACCCC	5160
CCTGTGACA	GCCGCCACCA	GCCTCACGTG	GCCACCTCTG	TCTTCCCCCA	TGAAGGGCTG	5220
GCTCCCAGT	ATATATAAAC	CTCTCTGGAG	CTCGGGCATG	AGCCAGCAAG	GCCACCCATC	5280
CAGGCACCTC	TCAGCACAGC	AGAGCTTCC	AGAGGAAGCC	TCACCAAGCC	TCTGCAATGA	5340
GGTTCTCTG	TGACAGTGTG	TGCAGCTTTG	GGCCTGAGAT	GCCAGCTGTC	CAGCTGCTGC	5400
TTCTGGCCTG	CCTGGTGTGG	GATGTGGGGG	CCAGGACAGC	TCAGCTCAGG	AAGGCCAATG	5460
ACCAGAGTGG	CCGATGCCAG	TATACCTTCA	GTGTGGCAG	TCCAATGAA	TCCAGCTGCC	5520
CAGAGCAGAG	CCAGGCCATG	TCAGTCATCC	ATAACTTACA	GAGAGACAGC	AGCACCCAAAC	5580
GCTTAGACCT	GGAGGCCACC	AAAGCTCGAC	TCAGCTCCT	GGAGAGCCTC	CTCCACCAAT	5640
TGACCTTGG	CCAGGCTGCC	AGGCCCCAGG	AGACCCAGGA	GGGGCTGCAG	AGGGAGCTGG	5700
GCACCCCTGAG	GGGGGAGCGG	GACCAGCTGG	AAACCCAAAC	CAGAGAGTTG	GAGACTGCCT	5760
ACAGCAACCT	CCTCCGAGAC	AAAGTCAGTTC	TGGAGGAAGA	GAAGAAGCGA	CTAAGGCAAG	5820
AAAATGAGAA	TCTGGCCAGG	AGGTTGGAAA	GCAGCAGCCA	GGAGGTAGCA	AGGCTGAGAA	5880
GGGGCCAGTG	TCCCCAGACC	CGAGACACTG	CTCGGGCTGT	GCCACCCAGGC	TCCAGAGAAG	5940
GTAAGAATGC	AGAGTGGGGG	GACTCTGAGT	TCAGCAGGTG	ATATGGCTCG	TAGTGAACCTG	6000
CTACAGGCAC	TCCAGGCCTC	CCTGCCCTTT	CTCCTAGAGA	CTGCACAGCT	ACCACAAGAC	6060
AGATGAATTA	AGGAAAGCAC	ACGATCACCT	TCAAGTATTA	CTAGTAATT	AGCTCCTGAG	6120
AGCTTCATTT	AGATTAGTGG	TTCAGAGTTC	TTGTGCCCT	CCATGTCAG		6169

## (2) INFORMATION FOR SEQ ID NO:4:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 926 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

AAGGTAGGCA	CATTGCCCTG	CAATTTATAA	TTTATGAGGT	GTCATTAT	GGAATTGTCA	60
AATATTAACA	AAAGTAGAGA	GACTACAATG	AACTCCAATG	TAGCCATAAC	TCAGGCCCAA	120
CTGTTATCAG	CACAGTCCAA	TCATGTTTA	TCTTCCCTTC	TCTGACCCCC	AACCCATCCC	180
CAGTCCTTAT	CTAAAATCAA	ATATCAAACA	CCATACTCTT	TGGGAGCCTA	TTTATTTAGT	240
TAGTTAGTT	TCAGACAGAG	TTTCTTTCTT	GTTCCCAAGC	TGGAGTACAA	TAGTGTAGTC	300
TCGGCTAAC	GCAATCTCCC	CCTCTTGTT	TCAAGCAATT	CTCCTGCCTC	AGTCTCCCAA	360
GAAGCTGGGA	TTATAGACAC	TCGGCACCCAC	ATCCAGCTAA	TTTTTTTGTG	TTTTAGAAAA	420
GACAGGGTT	CACCATGTG	GCCAGGCTGG	TTTCGAACTC	CTGACCTCAG	GTGATCCGCC	480
TGCCTCGGCC	TCCCAAAGTG	CTGGGATTAC	AGGCATGAGC	CACCAAGCCT	GGCCGGCAGC	540
CTATTTAAAT	GTCATCCTCA	ACATAGTCAA	TCCTTGGGCC	ATTTTTTCTT	ACAGTAAAAT	600
TTTGTCTCTT	TCTTTTAATC	AGTTTCTACG	TGGAATTG	ACACTTTGGC	CTTCCAGGAA	660
CTGAAGTCCG	AGCTAACTGA	AGTCTCTGCT	TCCCAGATT	TGAAGGAGAG	CCCACCTGGC	720
TATCTCAGGA	GTGGAGAGGG	AGACACCGGT	ATGAAGTAA	GTTCCTTC	TTTTGTGCC	780
ACGTGGCTT	TATTCATGTC	TAGTGTGTG	TTCAGAGAA	CAGTATAGGG	TAAATGCCCA	840
CCCAAGGGGG	AAATTAACCT	CCCTGGGAGC	AGAGGGAGGG	GAGGAGAAGA	GGAACAGAAC	900
TCTCTCTCTC	TCTCTGTAC	CCTTGT				926

## (2) INFORMATION FOR SEQ ID NO:5:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2099 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TGGCTCTGCC	AAGCTTCCGC	ATGATCATTG	TCTGTGTTG	GAAGATTATG	GATTAAGTGG	60
TGCTTCGTT	TCTTTCTGAA	TTTACCAAGGA	TGTGGAGAAC	TAGTTGGGT	AGGAGAGCCT	120
CTCACGCTGA	GAACAGCAGA	AACAATTACT	GGCAAGTATG	GTGTGTTGGAT	GCGAGACCCC	180
AAGCCCCACCT	ACCCCTACAC	CCAGGAGACC	ACGTGGAGAA	TGACACAGT	TGGCACGGAT	240
GTCCGCCAGG	TTTTTGAGTA	TGACCTCATC	AGCCAGTTA	TGCAAGGCTA	CCCTTCTAAG	300
GTTCACATAC	TGCCTAGGCC	ACTGAAAGC	ACGGGTGCTG	TGGTGTACTC	GGGGAGCCTC	360
TATTTCCAGG	GCGCTGAGTC	CAGAACTGTC	ATAAGATATG	AGCTGAATAC	CGAGACAGTG	420
AAGGCTGAGA	AGGAAATCCC	TGGAGCTGGC	TACCAAGGAC	AGTTCCCGTA	TTCTTGGGT	480
GGCTCACACGG	ACATTGACTT	GGCTGTGGAT	GAAGCAGGCC	TCTGGGTCAT	TTACAGCACC	540
GATGAGGCCA	AAGGTGCCAT	TGTCCTCTCC	AAACTGAACC	CAGAGAAATCT	GGAACCTCGAA	600
CAAACCTGGG	AGACAAACAT	CCGTAAGCAG	TCAGTCGCCA	ATGCCTTCAT	CATCTGTGGC	660
ACCTTGTACA	CCGTCAGCAG	CTACACCTCA	GCAGATGCTA	CCGTCAACTT	TGCTTATGAC	720
ACAGGCACAG	GTATCAGCAA	GACCCCTGACC	ATCCCATTCA	AGAACCGCTA	TAAGTACAGC	780
AGCATGATTG	ACTACAACCC	CCTGGAGAAG	AAGCTCTTTG	CCTGGGACAA	TCTGAACATG	840
GTCACTTATG	ACATCAAGCT	CTCCAAGATG	TGAAAAGCCT	CCAAAGCTGA	CAGGCAATGG	900
CAGAAGGAGA	TGCTCAGGGC	TCCCTGGGGG	AGCAGGGTGA	AGGGAGAGCC	AGCCAGCCAG	960
GGCCCAGGCA	GCTTGACTG	CTTCCAAGT	TTTCATTAAT	CCAGAAGGAT	GAACATGGTC	1020
ACCATCTAAC	TATTCAAGGA	TTGTAGTCTG	AGGGCGTAGA	CAATTTCATA	TAATAAATAT	1080
CCTTTATCTT	CTGTCAGCAT	TTATGGATG	TTTAATGACA	TAGTTCAAGT	TTTCTTGTGA	1140
TTTGGGGCAA	AAGCTGTAAG	GCATAATAGT	CTTTTCCTGA	AAACCATTGC	TCTTGCATGT	1200
TACATGGTTA	CCACAAGCCA	CAATAAAAAG	CATAACTTCT	AAAGGAAGCA	GAATAGCTCC	1260
TCTGGCCAGC	ATCGAATATA	AGTAAGATGC	ATTTACTACA	GTGGCTTCT	AATGCTTCAG	1320
ATAGAATACA	GTTGGGTCTC	ACATAACCCCT	TACATTGTGA	AATAAAATT	TCTTACCCAA	1380
CGTTCTCTTC	CTTGAACCTT	GTGGGAATCT	TTGCTTAAGA	GAAGGATATA	GATTCCAACC	1440
ATCAGGTAAT	TCCTTCAGGT	TGGGAGATGT	GATTGCGAGA	TGTTAAAGT	GTGTGTGTGT	1500
GTGTGTGTGT	GTGTGTAACT	GAGAGGCTTG	TGCCTGGTT	TGAGGTGCTG	CCCAGGATGA	1560
CGCCAAGCAA	ATAGCGCATC	CACACTTTC	CACCTCCATC	TCCTGGTGCT	CTCGGCACTA	1620
CCGGAGCAAT	CTTTCCATCT	CTCCCCCTGAA	CCCACCCCT	ATTCAACCTA	ACTCCACTTC	1680
AGTTTGCTT	TGATTTTTT	TTTTTTTTT	TTTTTTTTT	GAGATGGGGT	CTCGCTCTGT	1740
CACCCAGGCT	GGAGTGCACT	GGCACGATCT	CGGCTCACTG	CAAGTTCCGC	CTCCCAGGTT	1800
CACACCATTG	TCCTGCCTCA	GCCTCCCAAG	TAGCTGGGAC	TACAGGCACC	TGCCACCAAG	1860
CCTGGCTAAT	TTTTTTTTT	TCCAGTGAAG	ATGGGTTTCA	CCATGTTAGC	CAGGATGGTC	1920
TCGATCTCCT	GACCTTGTCA	TCCACCCACC	TTGGCCCTCCC	AAAGTGCTGG	GATTACAGGC	1980
GTGAGGCCACC	ACGCCAGCC	CCTCCACTTC	AGTTTTTATC	TGTCACTCAGG	GGTATGAATT	2040
TTATAAGCCA	CACCTCAGGT	GGAGAAAGCT	TGATGCATAG	CTTGAGTATT	CTATACTGT	2099

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TGAGGCTTCC TCTGGAAAC

19

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

20

TGAAATCAGC ACACCACTAG

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

21

GCACCCATAC CCCAATAATA G

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

20

AGAGTTCCCC AGATTTCACC

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

20

ATCTGGGGAA CTCTTCTCAG

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

19

TACAGTTGTT GCAGATAACG

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

21

ACAAACGTATC TGCAACAACT G

## (2) INFORMATION FOR SEQ ID NO:13:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

TCAGGCTTAA CTGCAGAACCC

20

## (2) INFORMATION FOR SEQ ID NO:14:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

TTGGTTCTGC AGTTAACGCC

19

## (2) INFORMATION FOR SEQ ID NO:15:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

AGCAGCACAA GGGCAATCC

19

## (2) INFORMATION FOR SEQ ID NO:16:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

ACAGGGCTAT ATTGTGGG

18

## (2) INFORMATION FOR SEQ ID NO:17:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CCTGAGATGC CAGCTGTCC

19

## (2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 20 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CTGAAGCATT AGAACGCCAAC

20

## (2) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 20 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

ACCTTGGACC AGGCTGCCAG

20

## (2) INFORMATION FOR SEQ ID NO:20:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 19 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

AGGTTTGTTC GAGTTCCAG

19

## (2) INFORMATION FOR SEQ ID NO:21:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 20 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

ACAATTACTG GCAAGTATGG

20

## (2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 19 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CCTTCTCAGC CTTGCTACC

19

## (2) INFORMATION FOR SEQ ID NO:23:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

ACACCTCAGC AGATGCTACC

20

- (2) INFORMATION FOR SEQ ID NO:24:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 19 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

ATGGATGACT GACATGGCC

19

- (2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 19 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

AAGGATGAAC ATGGTCACC

19

- (2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1548 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

AGAGCTTCC	AGAGGAAGCC	TCACCAAGCC	TCTGCAATGA	GGTTCTTCTG	TGCACGTTGC	60
TGCAGCTTTG	GGCCTGAGAT	GCCAGCTGTC	CAGCTGCTGC	TTCTGGCCTG	CCTGGTGTGG	120
GATGTGGGGG	CCAGGACAGC	TCAGCTCAGG	AAGGCCAATG	ACCAGAGTGG	CCGATGCCAG	180
TATACCTTCA	GTGTGGCCAG	TCCCCAATGAA	TCCAGCTGCC	CAGAGCAGAG	CCAGGCCATG	240
TCAGTCATCC	ATAACTTACA	GAGAGACAGC	AGCACCCAAC	GCTTAGACCT	GGAGGCCACC	300
AAAGCTCGAC	TCAGCTCCCT	GGAGAGCCTC	CTCCACCAAT	TGACCTTGGA	CCAGGCTGCC	360
AGGCCCCAGG	AGACCCAGGA	GGGGCTGCAG	AGGGAGCTGG	GCACCCCTGAG	GCGGGAGCGG	420
GACCAGCTGG	AAACCCAAAC	CAGAGAGTTG	GAGACTGCC	ACAGCAACCT	CCTCCGAGAC	480
AAGTCAGTTC	TGGAGGAAGA	GAAGAAGCGA	CTAAGGCAAG	AAAATGAGAA	TCTGGCCAGG	540
AGGTTGGAAA	GCAGCAGCCA	GGAGGTAGCA	AGGCTGAGAA	GGGGCCAGTG	TCCCCAGACC	600
CGAGACACTG	CTCGGGCTGT	GCCACCAGGC	TCCAGAGAAAG	TTTCTACGTG	GAATTGGAC	660
ACTTTGGCCT	TCCAGGAACT	GAAGTCCGAG	CTAACTGAAG	TTCTCTGCTTC	CCGAATTGG	720
AAGGAGAGCC	CATCTGGCTA	TCTCAGGAGT	GGAGAGGGAG	ACACCGGATG	TGGAGAACTA	780
GTTTGGGTAG	GAGAGCCTCT	CACGCTGAGA	ACAGCAGAAA	CAATTACTGG	CAAGTATGGT	840
GTGTGGATGC	GAGACCCCAA	GCCCACCTAC	CCCTACACCC	AGGAGACAC	GTGGAGAAC	900
GACACAGTTG	GCACGGATGT	CCGCCAGGTT	TTTGAGTATG	ACCTCATCAG	CCAGTTATG	960
CAGGGCTACC	CTTCTAAGGT	TCACATACTG	CCTAGGCCAC	TGGAAAGCAC	GGGTGCTGTG	1020
GTCAGTCGG	GGAGCCTCTA	TTTCCAGGGC	GCTGAGTCCA	GAACGTGTCAT	AAGATATGAG	1080

CTGAATACCG AGACAGTGAA GGCTGAGAAG GAAATCCCTG GAGCTGGCTA CCACGGACAG	1140
TTCCCGTATT CTTGGGGTGG CTACACGGAC ATTGACTTGG CTGTGGATGA AGCAGGCCTC	1200
TGGGTCAATT ACAGCACCGA TGAGGCCAAA GGTGCCATTG TCCCTCTCAA ACTGAACCCA	1260
GAGAACATCGG AACTCGAACAA AACCTGGGAG ACAAACATCC GTAAGCAGTC AGTCGCCAAT	1320
GCCTTCATCA TCTGTGGCAC CTTGTACACC GTCAGCAGCT ACACCTCAGC AGATGCTACC	1380
GTCAACTTTG CTTATGACAC AGGCACAGGT ATCAGCAAGA CCCTGACCAT CCCATTCAAG	1440
AACCGCTATA AGTACAGCAG CATGATTGAC TACAACCCCC TGGAGAAGAA GCTCTTGCC	1500
TGGGACAAC TGAACATGGT CACTTATGAC ATCAAGCTCT CCAAGATG	1548

## (2) INFORMATION FOR SEQ ID NO:27:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 178 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Thr Gly Ala Val Val Tyr Ser Gly Ser Leu Tyr Phe Gln Gly Ala Glu  
   1                         5                         10                         15  
   Ser Arg Thr Val Ile Arg Tyr Glu Leu Asn Thr Glu Thr Val Lys Ala  
   20                         25                         30  
   Glu Lys Glu Ile Pro Gly Ala Gly Tyr His Gly Gln Phe Pro Tyr Ser  
   35                         40                         45  
   Trp Gly Gly Tyr Thr Asp Ile Asp Leu Ala Val Asp Glu Ala Gly Leu  
   50                         55                         60  
   Trp Val Ile Tyr Ser Thr Asp Glu Ala Lys Gly Ala Ile Val Leu Ser  
   65                         70                         75                         80  
   Lys Leu Asn Pro Glu Asn Leu Glu Leu Glu Gln Thr Trp Glu Thr Asn  
   85                         90                         95  
   Ile Arg Lys Gln Ser Val Ala Asn Ala Phe Ile Ile Cys Gly Thr Leu  
   100                         105                         110  
   Tyr Thr Val Ser Ser Tyr Thr Ser Ala Asp Ala Thr Val Asn Phe Ala  
   115                         120                         125  
   Tyr Asp Thr Gly Thr Gly Ile Ser Lys Thr Leu Thr Ile Pro Phe Lys  
   130                         135                         140  
   Asn Arg Tyr Lys Tyr Ser Ser Met Ile Asp Tyr Asn Pro Leu Glu Lys  
   145                         150                         155                         160  
   Lys Leu Phe Ala Trp Asp Asn Leu Asn Met Val Thr Tyr Asp Ile Lys  
   165                         170                         175  
   Leu Ser

## (2) INFORMATION FOR SEQ ID NO:28:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 131 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Arg Phe Asp Leu Lys Thr Glu Thr Ile Leu Lys Thr Arg Ser Leu Asp  
   1                         5                                 10                         15  
   Tyr Ala Gly Tyr Asn Asn Met Tyr His Tyr Ala Trp Gly Gly His Ser  
   20                         25                                 30  
   Asp Ile Asp Leu Met Val Asp Glu Ser Gly Leu Trp Ala Val Tyr Ala  
   35                         40                                 45  
   Thr Asn Gln Asn Ala Gly Asn Ile Val Val Ser Arg Leu Asp Pro Val  
   50                         55                                 60  
   Ser Leu Gln Thr Leu Gln Thr Trp Asn Thr Ser Tyr Pro Lys Arg Xaa

65	70	75	80
Pro Gly Xaa Ala Phe Ile Ile Cys Gly Thr Cys Tyr Val Thr Asn Gly			
85	90	95	
Tyr Ser Gly Gly Thr Lys Val His Tyr Ala Tyr Gln Thr Asn Ala Ser			
100	105	110	
Thr Tyr Glu Tyr Ile Asp Ile Pro Phe Gln Asn Lys Leu Xaa Pro His			
115	120	125	
Phe Pro Cys			
130			

## (2) INFORMATION FOR SEQ ID NO:29:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 178 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Gly Thr Gly Gln Val Val Tyr Asn Gly Ser Ile Tyr Phe Asn Lys Phe	15		
1	5	10	15
Gln Ser His Ile Ile Ile Arg Phe Asp Leu Lys Thr Glu Thr Ile Leu			
20	25	30	
Lys Thr Arg Ser Leu Asp Tyr Ala Gly Tyr Asn Asn Met Tyr His Tyr			
35	40	45	
Ala Trp Gly Gly His Ser Asp Ile Asp Leu Met Val Asp Glu Asn Gly			
50	55	60	
Leu Trp Ala Val Tyr Ala Thr Asn Gln Asn Ala Gly Asn Ile Val Ile	80		
65	70	75	80
Ser Lys Leu Asp Pro Val Ser Leu Gln Ile Leu Gln Thr Trp Asn Thr			
85	90	95	
Ser Tyr Pro Lys Arg Ser Ala Gly Glu Ala Phe Ile Ile Cys Gly Thr			
100	105	110	
Leu Tyr Val Thr Asn Gly Tyr Ser Gly Gly Thr Lys Val His Tyr Ala			
115	120	125	
Tyr Gln Thr Asn Ala Ser Thr Tyr Glu Tyr Ile Asp Ile Pro Phe Gln			
130	135	140	
Asn Lys Tyr Ser His Ile Ser Met Leu Asp Tyr Asn Pro Lys Asp Arg	160		
145	150	155	160
Ala Leu Tyr Ala Trp Asn Asn Gly His Gln Thr Leu Tyr Asn Val Thr			
165	170	175	
Leu Phe			

## (2) INFORMATION FOR SEQ ID NO:30:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 177 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Gly Ala Gly Val Val Val His Asn Asn Asn Leu Tyr Tyr Asn Cys Phe	15		
1	5	10	15
Asn Ser His Asp Met Cys Arg Ala Ser Leu Thr Ser Gly Val Tyr Gln			
20	25	30	
Lys Lys Pro Leu Leu Asn Ala Leu Phe Asn Asn Arg Phe Ser Tyr Ala			
35	40	45	
Gly Thr Met Phe Gln Asp Met Asp Phe Ser Ser Asp Glu Lys Gly Leu			
50	55	60	

Trp Val Ile Phe Thr Thr Glu Lys Ser Ala Gly Lys Ile Val Val Gly  
 65 70 75 80  
 Lys Val Asn Val Ala Thr Phe Thr Val Asp Asn Ile Trp Ile Thr Thr  
 85 90 95  
 Gln Asn Lys Ser Asp Ala Ser Asn Ala Phe Met Ile Cys Gly Val Leu  
 100 105 110  
 Tyr Val Thr Arg Ser Leu Gly Pro Lys Met Glu Glu Val Phe Tyr Met  
 115 120 125  
 Phe Asp Thr Lys Thr Gly Lys Glu Gly His Leu Ser Ile Met Met Glu  
 130 135 140  
 Lys Met Ala Glu Lys Val His Ser Leu Ser Tyr Asn Ser Asn Asp Arg  
 145 150 155 160  
 Lys Leu Tyr Met Phe Ser Glu Gly Tyr Leu Leu His Tyr Asp Ile Ala  
 165 170 175  
 Leu

## (2) INFORMATION FOR SEQ ID NO:31:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 74 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Gly Val Val Tyr Ser Arg Leu Thr Glu Thr Leu Ala Gly Tyr Asn Asn  
 1 5 10 15  
 Tyr Ala Trp Gly Gly Asp Ile Asp Leu Val Asp Glu Gly Leu Trp Tyr  
 20 25 30  
 Thr Ala Gly Ile Val Ser Lys Leu Pro Leu Gln Thr Trp Thr Lys Ala  
 35 40 45  
 Phe Ile Ile Cys Gly Thr Leu Tyr Val Thr Tyr Val Tyr Ala Tyr Thr  
 50 55 60  
 Ile Tyr Asp Tyr Asn Pro Lys Leu Tyr Leu  
 65 70

## (2) INFORMATION FOR SEQ ID NO:32:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 504 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: N-terminal

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Met Arg Phe Phe Cys Ala Arg Cys Cys Ser Phe Gly Pro Glu Met Pro  
 1 5 10 15  
 Ala Val Gln Leu Leu Leu Ala Cys Leu Val Trp Asp Val Gly Ala  
 20 25 30  
 Arg Thr Ala Gln Leu Arg Lys Ala Asn Asp Gln Ser Gly Arg Cys Gln  
 35 40 45  
 Tyr Thr Phe Ser Val Ala Ser Pro Asn Glu Ser Ser Cys Pro Glu Gln  
 50 55 60  
 Ser Gln Ala Met Ser Val Ile His Asn Leu Gln Arg Asp Ser Ser Thr  
 65 70 75 80  
 Gln Arg Leu Asp Leu Glu Ala Thr Lys Ala Arg Leu Ser Ser Leu Glu  
 85 90 95  
 Ser Leu Leu His Gln Leu Thr Leu Asp Gln Ala Ala Arg Pro Gln Glu  
 100 105 110

Thr Gln Glu Gly Leu Gln Arg Glu Leu Gly Thr Leu Arg Arg Glu Arg  
 115 120 125  
 Asp Gln Leu Glu Thr Gln Thr Arg Glu Leu Glu Thr Ala Tyr Ser Asn  
 130 135 140  
 Leu Leu Arg Asp Lys Ser Val Leu Glu Glu Lys Lys Arg Leu Arg  
 145 150 155 160  
 Gln Glu Asn Glu Asn Leu Ala Arg Arg Leu Glu Ser Ser Ser Gln Glu  
 165 170 175  
 Val Ala Arg Leu Arg Arg Gly Gln Cys Pro Gln Thr Arg Asp Thr Ala  
 180 185 190  
 Arg Ala Val Pro Pro Gly Ser Arg Glu Val Ser Thr Trp Asn Leu Asp  
 195 200 205  
 Thr Leu Ala Phe Gln Glu Leu Lys Ser Glu Leu Thr Glu Val Pro Ala  
 210 215 220  
 Ser Arg Ile Leu Lys Glu Ser Pro Ser Gly Tyr Leu Arg Ser Gly Glu  
 225 230 235 240  
 Gly Asp Thr Gly Cys Gly Glu Leu Val Trp Val Gly Glu Pro Leu Thr  
 245 250 255  
 Leu Arg Thr Ala Glu Thr Ile Thr Gly Lys Tyr Gly Val Trp Met Arg  
 260 265 270  
 Asp Pro Lys Pro Thr Tyr Pro Tyr Thr Gln Glu Thr Thr Trp Arg Ile  
 275 280 285  
 Asp Thr Val Gly Thr Asp Val Arg Gln Val Phe Glu Tyr Asp Leu Ile  
 290 295 300  
 Ser Gln Phe Met Gln Gly Tyr Pro Ser Lys Val His Ile Leu Pro Arg  
 305 310 315 320  
 Pro Leu Glu Ser Thr Gly Ala Val Val Tyr Ser Gly Ser Leu Tyr Phe  
 325 330 335  
 Gln Gly Ala Glu Ser Arg Thr Val Ile Arg Tyr Glu Leu Asn Thr Glu  
 340 345 350  
 Thr Val Lys Ala Glu Lys Glu Ile Pro Gly Ala Gly Tyr His Gly Gln  
 355 360 365  
 Phe Pro Tyr Ser Trp Gly Tyr Thr Asp Ile Asp Leu Ala Val Asp  
 370 375 380  
 Glu Ala Gly Leu Trp Val Ile Tyr Ser Thr Asp Glu Ala Lys Gly Ala  
 385 390 395 400  
 Ile Val Leu Ser Lys Leu Asn Pro Glu Asn Leu Glu Leu Glu Gln Thr  
 405 410 415  
 Trp Glu Thr Asn Ile Arg Lys Gln Ser Val Ala Asn Ala Phe Ile Ile  
 420 425 430  
 Cys Gly Thr Leu Tyr Thr Val Ser Ser Tyr Thr Ser Ala Asp Ala Thr  
 435 440 445  
 Val Asn Phe Ala Tyr Asp Thr Gly Thr Gly Ile Ser Lys Thr Leu Thr  
 450 455 460  
 Ile Pro Phe Lys Asn Arg Tyr Lys Tyr Ser Ser Met Ile Asp Tyr Asn  
 465 470 475 480  
 Pro Leu Glu Lys Lys Leu Phe Ala Trp Asp Asn Leu Asn Met Val Thr  
 485 490 495  
 Tyr Asp Ile Lys Leu Ser Lys Met  
 500

## (2) INFORMATION FOR SEQ ID NO:33:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 20 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CAAACAGACT TCCGGAAGGT

## (2) INFORMATION FOR SEQ ID NO:34:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5271 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

ATCTTTGTTCA	AGTTTACCTC	AGGGCTATTAA	TGAAATGAAA	TGAGATAACC	AATGTGAAAG	60
TCCTATAAAC	TGTATAGCCT	CCATTCCGGAT	GTATGTCCTT	GGCAGGGATGA	TAAAGAATCA	120
GGAAGAAGGA	GTATCCACGT	TAGCCAAGTG	TCCAGGCTGT	GTCTGCTCTT	ATTTTAGTGA	180
CAGATGTGCA	TCCTGACAGA	AGCTATTCTT	CAGGAAACAT	CACATCCAAT	ATGGTAAATC	240
CATCAAACAG	GAGCTAAGAA	ACAGGAATGA	GATGGGCACT	TGCCCAAGGA	AAAATGCCAG	300
GAGAGCAAAT	AATGATGAAA	AATAAACTTT	TCCCTTGTGTT	TTAATTTCAT	GGAAAAAAATG	360
ATGAGGACCA	AAATCAATGA	ATAAGGAAAA	CAGCTCAGAA	AAAAGATGTT	TCCAAATTGG	420
TAATTAAAGTA	TTTGTTCCTT	GGGAAGAGAC	CTCCATGTGA	GCTTGATGGG	AAAATGGAA	480
AAACGTCAAA	AGCATGATCT	GATCAGATCC	CAAAGTGGAT	TATTATTATA	AAAACAGAT	540
GGCATCACTC	TGGGGAGGC	AGTTCAAGGAA	GGTCATGTGA	GCAAAGGACA	TAACAATAAC	600
AGCAAAATCA	AAATTCCGCA	AATGCAGGAG	AAAATGGGG	ACTGGGAAAG	CTTTCTAAC	660
AGTGTATTAGG	CAGTTGACCA	TGTTCGCAAC	ACCTCCCCGT	CTATACCCAGG	GAACACAAAA	720
ATTGACTGGG	CTAAGCCTGG	ACTTTCAAGG	AAAATATGAA	AAACTGAGAG	AAAACAAAAA	780
GACATGGTTA	AAAGGCAACC	AGAACATTGT	GAGCCTTCAA	AGCAGCAGTG	CCCCTCAGCA	840
GGGACCCCTGA	GGCATTTCGCC	TTTAGGAAGG	CCAGTTTCT	TAAGGAATCT	TAAGAAACTC	900
TTGAAAGATC	ATGAATTTTA	ACCATTTTAA	GTATAAAACA	AATATGCGAT	GCATAATCAG	960
TTTAGACATG	GGTCCCAATT	TTATAAAGTC	AGGCATACAA	GGATAACGTG	TCCCAGCTCC	1020
GGATAGGTCA	GAAATCATTA	GAAATCACTG	TGTCCCCATC	CTAACTTTT	CAGAATGATC	1080
TGTCTAGCC	CTCACACACA	GGCCCGATGT	GTCTGACCTA	CAACCACATC	TACAACCCAA	1140
GTGCTCAAC	CATTGTTAAC	GTGTCACTC	AGTAGGTCCC	ATTACAAATG	CCACCTCCCC	1200
TGTGCAGCCC	ATCCCGCTCC	ACAGGAAGTC	TCCCCACTCT	AGACTTCTGC	ATCACCGATGT	1260
TACAGCCAGA	AGCTCCGTGA	GGGTGAGGGT	CTGTGCTTA	CACTACCTG	TATGCTCTAC	1320
ACCTGAGCTC	ACTGCAACCT	CTGCCCTCCCA	GGTTCAAGCA	ATTCTCCTGT	CTCAGCCTCC	1380
CGCGTAGCTG	GGACTACAGG	CGCACGCCCG	GCTAATTTTT	GTATTGTTAG	TAGAGATGGG	1440
GTTTACCAT	ATTAGCCCGG	CTGGTCTTGA	ACTCCTGACC	TCAGGTGATC	CACCCACCTC	1500
AGCCTCTAA	AGTGTGGGA	TTACAGGCAT	GAGTCACCGC	GCCCCGGCCAA	GGGTCACTGT	1560
TTAATAAGGA	ATAACTTGA	TGGTTTACTA	AACCAACAGG	GAAACAGACA	AAAGCTGTGA	1620
TAATTTCAAGG	GATTCTGGG	ATGGGAATG	GTGCCATGAG	CTGCCCTGCCT	AGTCCAGAC	1680
CACTGGCTCT	CATCACTTTC	TTCCCTCATC	CTCATTTCA	GGCTAAGTTA	CCATTCTATT	1740
CACCATGCTT	TTGTGGTAAG	CCTCCACATC	GTTAATGAAA	TAAGAGTATA	CATAAAACTAG	1800
TTCCATTGTTG	GGCCATCTGT	GTGTGTGTAT	AGGGGAGGAG	GGCATACCCC	AGAGACTCCT	1860
TGAAGCCCCC	GGCAGAGGTT	TCCTCTCCAG	CTGGGGGAGC	CCTGCAAGCA	CCCGGGGTCC	1920
TGGGTGTCCT	GAGCAACCTG	CCAGCCCCGT	CCACTGGTTG	TTTGTTATC	ACTCTCTAGG	1980
GACCTGTTGC	TTTCTATTTC	TGTGTGACTC	GTTCATTCA	CCAGGCATT	ATTGACAATT	2040
TATTGAGTAC	TTATATCTGC	CAGACACCAG	AGACAAAATG	GTGAGCAAAG	CAGTCACTGC	2100
CCTACCTTCG	TGGAGGTGAC	AGTTCTCAT	GGAAAGACGTG	CAGAAGAAAA	TTAATAGCCA	2160
GCCAACCTAA	ACCCAGTGT	GAAAGAAAGG	AAATAAACAC	CATCTTGAAG	AATTGTGCGC	2220
AGCATCCCTT	AACAAGGCCA	CCTCCCTAGC	GCCCCCTGCT	GCCTCCATCG	TGCCCCGGAGG	2280
CCCCCAAGCC	CGAGTCCTCC	AAGCCTCCCTC	CTCCATCACT	CACAGCCTG	CAGCTGGCCT	2340
GCCTCGCTTC	CCGTGAATCG	TCCTGGTGA	TCTGAGCTGG	AGACTCCTTG	GCTCCAGGCT	2400
CCAGAAAGGA	AATGGAGAGG	GAAACTAGTC	TAACGGAGAA	TCTGGAGGGG	ACAGTGTTC	2460
CTCAGAGGGA	AAGGGGCTC	CACGTCCAGG	AGAATTCAG	GAGGTGGGGA	CTGCAGGGAG	2520
TGGGGACGCT	GGGGCTGAGC	GGGTGCTGAA	AGGCAGGAAG	GTGAAAAGGG	CAAGGCTGAA	2580
GCTGCCAGA	TGTTCACTG	TGTTACCGG	GCTGGGAGTT	TTCCGTTGC	TCCTGTGAGC	2640
CTTTTATCT	TTTCTCTGCT	TGGAGGGAGAA	GAAGTCTATT	TCATGAAGGG	ATGCACTTTC	2700
ATAAAGTCAG	CTGTTAAAT	TCCAGGGTGT	GCATGGGTTT	TCCTTCACGA	AGGCCTTTAT	2760
TTAATGGAA	TATAGGAAGC	GAGCTCATTT	CCTAGGGCGT	TAATTCA	AAGAAGTGAC	2820
TGGAGTCTT	TCTTTCTATG	CTTCTGGGCA	ACTACTCAGC	CCTGTGGTGG	ACTTGGCTTA	2880
TGCAAGACGG	TCGAAAACCT	TGGAATCAGG	AGACTCGGTT	TTCTTCTGG	TTCTGCCATT	2940
GGTTGGCTGT	GCGACCGTGG	GCAAGTGTCT	CTCCTCCCT	GGGCCATAGT	CTTCTCTGCT	3000
ATAAAGACCC	TTGCAGCTCT	CGTGTCTGT	GAACACTTCC	CTGTGATTCT	CTGTGAGGGG	3060

GGATGTTGAG AGGGGAAGGA GGCAGAGCTG GAGCAGCTGA	GCCACAGGGG	AGGTGGAGGG	3120
GGACAGGAAG GCAGGCAGAA GCTGGGTGCT	CCATCAGTCC	TCACTGATCA	3180
CAGGACCGAG AGCCACAATG CTTCAGGAAA	GCTCAATGAA	CCCAACAGCC	3240
TCCCTAAGCA TAGACAATGG CATTGCCAA	TAACCAAAAAA	GAATGCAGAG	3300
GGTAGCTTT GCCTGGCATT	CAAAAATGG	GCCAGAGCAA	3360
TTAAACTTT CACCCCTGACC	AGCACCCCCAC	GTGAGAAATG	3420
AGTGACCTGC AGGCCAGGGG	AGGAGAAGAA	CCAGCTCAGC	3480
ACAGATTCA TCAAGGGCAG	TGGGAATTGA	AGTGAAGAGGG	3540
GTTCTAGGAG GCAGGGCTAT	ATTGTGGGGG	AAAGAGAGGG	3600
CCTGATTCT AATACTATAT	TTTCCCTTA	ATAGTGTATG	3660
GTAGTAATG AGGCTGTAAG	ATTACTTAGT	CCACAGGGAT	3720
GGAGTTAGCA GCACAAGGGC	AATCCCCTT	TATAGTCCAC	3780
TAAAGCCAAA CAGATTCAAG	CCTAGGTCTT	GTTCAAGGGA	3840
CATTTCAGCG ATGTTTACTA	TCTGAGTCAG	AGTCGGGAGA	3900
TAAACAAACA CCCAGTTGTA	AATGTCCTAA	AAGTCAAG	3960
AGAATAGAAT CTTAGAGCA	AACTGTTT	TTTCTCTGT	4020
AGTTGGAAA TATTTACTTC	ACAAGTATTG	TTCTCTGT	4080
TGCTCAAAGG CAATCATTAT	TTCAGTGGC	TTCTCTGT	4140
TTATTGGCTA TTGCCATTG	CTTTTGTTT	TTCTCTGT	4200
GGATTATTAA CCTACAGTCC	AGAAAGCCTG	TTCTCTGT	4260
TGTTTTTAC ACCCTCTAAC	AAATTAAAC	TTCTCTGT	4320
CTCAAAGTGG TAATAACAGT	ACCTGTGATT	TTCTCTGT	4380
TTATACTATA TTACAGTTGT	TGCAGATAAC	TTCTCTGT	4440
CTTTGAAATT AGACCTCTG	CTGGATCTTG	TTCTCTGT	4500
ATTTTGATAT TTGATAATC	ATATTCTATT	TTCTCTGT	4560
ATATATTGAA AAACATCTT	CTGAGAAGAG	TTCTCTGT	4620
CATGCACACA CACAGATTA	GAACGTGATT	TTCTCTGT	4680
TGCAAGACTG AAATTAGAAA	GTCTCCCAA	TTCTCTGT	4740
AGGGGGAAA TCTGCCGCTT	CTATAGGAAT	TTCTCTGT	4800
CTTGTGTTCT GGCTGGCTGT	TATTTTCTC	TTCTCTGT	4860
GGATCTCCAG TTCCCTAGCAT	AGTGCCTGGC	TTCTCTGT	4920
TGAATGGAAA TATAAACTAG	AAATATATCC	TTCTCTGT	4980
TGTAAGTGTG TGACGTGTG	TGTGTGTG	TTCTCTGT	5040
TAGGAACAT TATTGGGTA	TGGGTGCTAA	TTCTCTGT	5100
CAAACAGACT TCTGGAAAGGT	TATTTCTAA	AAAGAAACTC	5160
CCTGTGACA GCCCCACCCA	GCCTCACGTG	GGCAGCGTGA	5220
GCTCCCCAGT ATATATAAAC	CTCTCTGGAG	AGGCAACCCC	
	CTCGGGCATG	TGAAGGGCTG	
	AGCCAGCAAG G		

## (2) INFORMATION FOR SEQ ID NO:35:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 19 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

AACTATTATT GGGGTATGG

23

## (2) INFORMATION FOR SEQ ID NO:36:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 19 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

TTGGTGAGGC TTCCTCTGG

19

## (2) INFORMATION FOR SEQ ID NO:37:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH:
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

AACTAT TATTGGGTA TGGGTGCATA AATTGGGATG TTCTTTTAA AAAGAAACTC	5100
CAAACAGACT TCTGGAAGGT TATTTCTAA GAATCTTGCT GGCAGCGTGA AGGCAACCCC	5160
CCTGTGCACA GCCCCACCCA GCCTCACGTG GCCACCTCTG TCTTCCCCCA TGAAGGGCTG	5220
GCTCCCCAGT ATATATAAAC CTCTCTGGAG CTCGGGCATG AGCCAGCAAG GCCACCCATC	5280
CAGGCACCTC TCAGCACAGC AGAGCTTTCC AGAGGAAGCC TCACCAA	

## (2) INFORMATION FOR SEQ ID NO:38:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH:
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

AACTAT TATTGGGTA TGGGTGCATA AATTGGGATG TTCTTTTAA AAAGAAACTC	5100
CAAACAGACT TCTGGAAGGT TATTTCTAA GAATCTTGCT GGCAGCGTGA AGGCAACCCC	5160
CCTGTGCACA GCCCCACCCA GCCTCACGTG GCCACCTCTG TCTTCCCCCA TGAAGGGCTG	5220
GCTCCCCAGT ATATATAAAC CTCTCTGGAG CTCGGGCATG AGCCAGCAAG G	

# INTERNATIONAL SEARCH REPORT

International Application No  
**PCT/US 00/00559**

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7	C12Q1/68	A61P27/06	C12N5/10	C12N15/85	A61K31/7088
	A61K48/00				

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q A61P C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>NGUYEN TH D ET AL: "Gene structure and properties of TIGR, an olfactomedin-related glycoprotein cloned from glucocorticoid-induced trabecular meshwork cells"</p> <p>JOURNAL OF BIOLOGICAL CHEMISTRY, US, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 273, no. 11, 13 March 1998 (1998-03-13), pages 6341-6350-6350, XP002132916</p> <p>ISSN: 0021-9258</p> <p>the whole document</p> <p>---</p> <p>WO 98 44107 A (UNIVERSITY OF CALIFORNIA ;HUANG WEIDONG (US); NGUYEN THAI D (US);)</p> <p>8 October 1998 (1998-10-08)</p> <p>the whole document</p> <p>---</p> <p>---</p>	1-111
X		1-111

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

Date of mailing of the international search report

25 May 2000

31/05/2000

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Müller, F

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/00559

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 32850 A (UNIV CALIFORNIA) 30 July 1998 (1998-07-30) the whole document —	1-111
X	WO 96 14411 A (UNIV CALIFORNIA) 17 May 1996 (1996-05-17) see whole doc. esp. claims —	1-111
X	KUBOTA R ET AL: "Genomic organisation of the human myocilin gene (MYOC) responsible for primary open angle glaucoma" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, US, ACADEMIC PRESS INC. ORLANDO, FL, vol. 242, no. 242, 1998, pages 396-400-400, XP002120488 ISSN: 0006-291X se whole doc. esp. fig. 2 —	70
P,X	WO 99 16898 A (ANCTIL JEAN LOUIS ;COTE GILLES (CA); MORISSETTE JEAN (CA); RAYMOND) 8 April 1999 (1999-04-08) the whole document —	1-111

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Information on patent family members			International Application No PCT/US 00/00559	
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